FDA Executive Summary

Prepared for the

April 8, 2013 meeting of the

Ophthalmic Devices Advisory Panel

P030002/S027

Bausch + Lomb

Trulign™ Toric Accommodating Posterior Chamber Intraocular Lens (IOL)

Model AT-50T/AT-52T

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1. Introduction

The information in this document comprises FDA's executive summary of premarket approval (PMA) application P030002/S27 from Bausch + Lomb for their Models AT-50T/AT-52T Toric Accommodating Posterior Chamber Intraocular lens (IOL). Included is a description of the device, pre-clinical testing information, an overview of the pivotal clinical investigation conducted by Bausch + Lomb with respect to the clinical study protocol as well as the endpoints, results and statistical analyses.

Intraocular lenses (IOLs) are classified as Class III devices and are indicated for the visual correction of aphakia secondary to the removal of a cataractous lens in adult patients.

The following types of IOLs have received PMA approval for the visual correction of aphakia following cataract surgery. These are listed below, along with the standardized definitions in FDA recognized International Organization for Standardization (ISO) 11979-1 and the specific international and national standards associated with them that contain clinical requirements and guidance. A "recognized consensus standard" is a consensus standard that FDA has evaluated and recognized for use in satisfying a regulatory requirement and for which FDA has published a notice in the Federal Register. The general preclinical requirements for these IOLs are provided in ISO 11979-1, 2, 3, 4, 5, 6, 8 and ANSI Z80.7 standards.

- Monofocal IOLs - intraocular lens with two rotationally symmetric optical surfaces having one primary focus. FDA recognized ISO 11979-7 and ANSI Z80.7 standards describe the specific requirements for monofocal IOLs.

- Multifocal IOLs - intraocular lens with two rotationally symmetric optical surfaces having two or more foci. FDA recognized ISO 11979-9 and ANSI Z80.12 standards describe the specific requirements for multifocal IOLs.

- Toric IOLs - intraocular lens with at least one of the two surfaces (anterior or posterior) having maximum and minimum radii of curvature perpendicular to each other. ANSI Z80.30 describes the specific requirements for toric IOLs.

- Accommodating IOLs - intraocular lens which provides continuous focusing from far point to near point by changing the dioptric power of the eye. ANSI and ISO have been developing standards for accommodating IOLs for a number of years. While there are currently no published standards that describe the specific requirements for accommodating IOLs, significant progress has been made in describing recommended elements of the clinical investigation such as sample size, investigation duration, performance outcomes, and minimum accommodative amplitude.

The FDA recognized ISO 22979 technical report describes requirements for modifications to monofocal and multifocal IOLs that have undergone a clinical investigation. IOL models that have undergone a clinical investigation with at least 100 subjects are considered "parent" IOLs for the purposes of the technical report. This technical report does not provide guidance on modifications to toric or accommodating IOLs.

Currently, there are two approved toric IOLs (STAAR Surgical Company STAAR Toric IOLs and Alcon AcrySof Toric IOLs). Only one accommodating IOL platform has been approved to date (Crystalens Accommodating Posterior Chamber IOL, several models). However, currently there is no approved IOL that is designed to provide both accommodation and correction for astigmatism. Hence, the device being brought for panel consideration is a "first of a kind."

Reviewer comment: *The Models AT-50T/AT-52T Toric Accommodating IOLs are a modification of the Applicant's PMA approved Models AT-50/AT-52 Accommodating IOLs. The modifications are the addition of the toric surface to the IOL optic and alignment marks. The FDA recognized ISO 22979 describes requirements for modifications to IOLs that have undergone a clinical investigation and are therefore considered a parent IOL for monofocal and multifocal IOLs. However, the technical report does not include modifications to accommodating or toric IOLs.*

2. Device Description

The Bausch & Lomb Trulign™ Toric Accommodating Posterior Chamber Intraocular Lens (IOL), Model AT-50T/AT-52T is a modified plate haptic lens with hinges across the plates adjacent to the optic. The Trulign™ Toric lens Models AT50T/AT52T has a spherical front (anterior) surface with alignment marks and a Toric back (posterior) surface. The available cylindrical powers are 1.25, 2.00 and 2.75 D (at the IOL plane).

The Trulign™ Toric IOL (Figure 1) is a multi-piece lens with a biconvex silicone optic and fused polyimide loops. The lens has an axis mark on the anterior surface, indicating the flat meridian of the optic and a toric posterior surface, with an overall diameter of 11.5 mm (Models AT50T, BL1AT and BL1UT), and 12.0 mm (Models AT52T, BL2AT and BL2UT), and an optic body diameter of 5.00 mm.

Models AT50T, AT52T, BL1AT and BL2AT are molded from a silicone elastomer, [redacted] which has a 10% UV cutoff value of 350 nm. Models BL1UT and BL2UT are molded from a silicone elastomer, [redacted] with [redacted] UV chromophore, which has a 10% UV cutoff value at 400 nm. These are the same materials approved for the parent (non-toric) Trulign™ IOL models.

The Trulign™ Toric, Model AT50T/AT52T IOL is a modification to the currently approved Crystalens Five-O IOL (Models AT50SE and AT52SE). The only difference between the proposed Trulign™ Toric (AT50T/AT52T) and the Crystalens Five-O (AT50SE/AT52SE) is in the incorporation of a toroidal posterior optic surface.

Reviewer's Comment*: Bausch + Lomb is seeking approval for lens models with 11.5 and 12.0 mm optics However, we believe that the 12.0 mm lens may not be comparable to the 11.5mm with regard to the rotational stability. Since only a small number of subjects were implanted with the 12.0 mm optic lens (in violation of the approved protocol), FDA does not believe adequate data were provided to establish the rotational stability of this lens model.*

The Applicant developed a Web-Based Toric Calculator (WBTC) as part of the device to aid surgeons in determining the appropriate toric model to implant. This Toric Calculator can be accessed via the Internet and is used to calculate the predicted postoperative corneal astigmatism using preoperative keratometry, phaco/insertion incision location, and predicted magnitude of surgically induced astigmatism (SIA) inputs entered by the physician. The calculator accounts for SIA, incision location, and the subject's preoperative corneal astigmatism, and determines the Toric IOL cylinder power needed and placement orientation to best correct a subject's predicted postoperative corneal astigmatism. The calculator rejects gross entry errors, and gives an accurate recommendation on IOL cylinder power.

3. Proposed Indications for Use

The Trulign™ Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia secondary to the removal of a cataractous lens in adult patients with and without presbyopia and to reduce the effects of preoperative corneal astigmatism on postoperative refraction following cataract surgery. The Trulign™ Toric lens provides approximately one diopter of monocular accommodation which allows for near, intermediate, and distance vision without spectacles.

4. Regulatory History

4.1. Crystalens Model AT-45

Crystalens Model AT-45 Accommodating Posterior Chamber IOL, was the subject of P030002. The Ophthalmic Devices Panel reviewed the clinical data at a meeting on May 23, 2003, and recommended approval. P030002 was approved on November 14, 2003. The approved indications for use were "primary implantation in the capsular bag of the eye for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed and is intended to provide near, intermediate and distance vision without spectacles. The Crystalens IOL provides approximately one diopter of monocular accommodation."

The Crystalens Model AT-45 IOL is not designed to correct for astigmatism.

4.2. Trulign™ Toric Accommodating Posterior Chamber Intraocular Lens

Bausch + Lomb received approval under IDE G990163/S023 for a clinical trial [redacted]

[redacted]

The Applicant received approval on March 22, 2010 (S049) for implementation of a modified pivotal protocol (Study 650) involving implantation on Model AT-50T (Crystalens Toric Accommodating IOL) and AT-50 (control spherical Crystalens), both of which have a 5.0 mm optic. The investigation was limited to 6 institutions and 230 U.S. subjects (monocular implantation, 150 investigational and 80 control subjects). Data collected under this IDE are presented in this application.

***Reviewer's Comment**: A total of four additional sites were approved under Supplements 50 and 55. The total number of sites for the study was 10. Note that there was one out-of-U.S. site in the pivotal trial. Bausch + Lomb received approval in on December 17, 2010 under G990163/S53 for an expansion of the spherical power range from 18-26 D to 16-27 D.*

5. Pre-Clinical Studies

5.1. Biocompatibility

The Trulign™ Models AT50T/AT52T that were clinically studied are made of the same silicone elastomer, [redacted], as the Crystalens Model AT45. Testing was performed on the Crystalens Model AT-45 (non-toric) IOL (or representative samples of the finished device), and submitted in P030002. The testing was conducted in conformance with relevant parts of ISO 10993 and ISO 11979 and included cytotoxicity testing, acute systemic toxicity testing, irritation/sensitization testing, muscle implant studies, genotoxicity testing material-mediated pyrogen testing, testing for extractables by exhaustive extraction, hydrolytic stability testing and Nd:YAG laser testing. The FDA reviewers found this testing to be adequate.

The proposed Models BL1UT/BL2UT are made from a silicone elastomer, [redacted]. This is the same material used in the The Crystalens UVAM Accommodating Posterior Chamber Intraocular Lens Models AO1UV and AO2UV, which were approved under P030002/S020. The biocompatibility data for the [redacted] were submitted in P030002/S020. The testing was conducted in conformance with relevant parts of ISO 10993 and ISO 11979 and included cytotoxicity testing, acute systemic toxicity testing, irritation/sensitization testing, muscle implant studies, genotoxicity testing material-mediated pyrogen testing, testing for extractables by exhaustive extraction, hydrolytic stability testing and Nd:YAG laser testing.

Tables 1-2 summarize the biocompatibility testing conducted on [redacted] respectively.

5.2. Sterilization, Packaging and Shelf Life

The Trulign™ Toric IOLs are packaged in packaging that includes a polycarbonate lens case and a steam sterilized double pouched and tamper-evident carton. Sterilization validation data were presented in P030002 and incorporated by Bausch + Lomb by reference.

Package integrity testing was conducted to verify adequate microbial barrier and included microbial barrier consisting of an aerosol challenge and shipping challenges consisting of visual inspection, bubble testing, and peel strength testing and qualification during shipping, drop testing and vibration testing.

Bausch + Lomb conducted shelf life testing to justify a shelf life of 5 years. FDA reviewers found the testing adequate to justify this shelf-life.

5.3. Engineering Bench Testing - Optical and Mechanical Properties for Toric Model AT50T/AT52T

The optical properties of Trulign™ Toric models lenses were tested according to ISO11979-2:1999 (Ophthalmic Implants-Intraocular Lenses-Part 2 Optical properties and test methods) and ANSI Z80.30 (Toric Intraocular Lenses). The mechanical properties were tested according to ISO 11979-3:2006(E) (Ophthalmic Implants – Intraocular Lenses: Mechanical properties and test methods).

The lens testing was performed using the fully processed and sterilized Trulign™ AT50T/AT52T manufactured from the Bausch + Lomb Rancho Cucamonga, CA manufacturing facility, using validated processes for model AT50T/AT52T.

The testing was completed on lenses representing the low, medium, and high diopter range (10.0D, 22.0D and 33.0D) at 1.25D, 2.0D, 2.75D cylinders for each diopter. The results of the testing demonstrate that the Trulign™ AT50T/AT52T models meet the ISO and ANSI standards for optical and mechanical properties as required per standards mentioned above.

5.4. Manufacturing

The Trulign™ Toric lenses are molded, tumbled, polished, deflashed, cleaned, measured, inspected and placed into the primary package (lens case, inner and outer pouch). The lenses are sterilized by autoclave (steam) and then placed into the secondary package (lens box with the Directions For Use (DFU), and other labeling materials).

The lenses then go through an optical inspection using the [redacted] which measures diopter, cylinder power, image quality and cylinder angle. This specific optical inspection method is new for the toric lenses and has been validated for its use with the toric lenses. Because the optical system used to measure non-toric lenses cannot measure toric lenses, the [redacted] was added to the process.

To demonstrate the functional delivery performance, testing was completed on Trulign™ Toric (Models AT50T and AT52T) Intraocular Lens (IOL) using the Crystalsert (CI-28) insertion device. Testing was completed in accordance with the requirements of ISO 11979-3: Ophthalmic Implants – Intraocular lenses: Mechanical properties and test methods. Testing consisted of cosmetic inspection, optical inspection, dimensional inspection and the measurement of sagitta both before and after inspection. The delivery testing was performed using fully processed and

sterilized Model AT50T/AT52T lenses supplied from product manufactured from the Rancho Cucamonga, CA manufacturing facility.

All Model AT50T/AT52T lens samples underwent functional delivery testing using the CI-28 Crystalsert Delivery System. FDA reviewers found the functional delivery testing satisfactory.

5.5. Software Validation

Bausch + Lomb has provided acceptable documentation demonstrating that they have developed the software for the Toric Calculator under an appropriate software development program; that they have performed a hazard analysis from both the patient's and user's standpoint, and addressed those hazards; and carried out an appropriate validation process. These procedures provide the foundation for assuring, to the extent possible, that the software will operate in a manner described in the specifications, and in no other way.

6. Clinical Data

6.1. Prior Clinical Studies

6.1.1. Clinical Trial to Support the Parent IOL (Crystalens Spherical Accommodating IOL)

The Crystalens Model AT-45 Accommodating Posterior Chamber IOL was approved on November 14, 2003 and the summary of safety and effectiveness (http://www.accessdata.fda.gov/cdrh_docs/pdf3/P030002b.pdf) contains a detailed summary of the clinical study. This section highlights some key aspects of the study.

The clinical trial was a prospective, nonrandomized study of 324 subjects followed for one year under IDE#G990163. Inclusion criteria required visual potential to be 20/30 or better in the operative eye, 1.00 D or less of corneal astigmatism, an intact capsular bag and zonules after cataract extraction and before implantation of the lens. The clinical effectiveness endpoint was visual performance at near, intermediate and distance.

The adverse events experienced during the clinical trial of the Crystalens IOL included persistent iritis (<1.0%), persistent cystoid macular edema (<1.0%), and cumulative cystoid macular edema (3.7%). The incidence of adverse events was comparable to or lower than the incidence reported in the historical control ("FDA grid", now known as the ISO Safety and Performance Endpoints) population. See Table 3. One case of lens explantation was secondary to anterior vault. Effectiveness outcomes are summarized below. For the subjects implanted bilaterally:

- 93.5% achieved bilateral uncorrected near visual acuities of 20/32 or better one year after surgery

- 100% of the subjects achieved bilateral uncorrected intermediate visual acuities of 20/32 or better one year after surgery

- 97.6% of the subjects achieved bilateral uncorrected distance visual acuities of 20/32 or better one year after surgery.

In a substudy, unilateral distance corrected visual acuities of 20/40 or better at near, intermediate and distance 3-6 months or more after surgery were reported in 88.4% of the subjects with the Crystalens IOL and 35.9% of the subjects implanted with the standard monofocal IOL.

Near visual acuity was the main outcome measure used to support accommodative effectiveness. Assessment of accommodative amplitude was performed on a small subset of five subjects implanted bilaterally (i.e., 10 eyes) with the Crystalens at a single clinical site and included subjective and objective accommodative assessments. There were no control eyes for comparison. This testing was performed in an effort to document the mechanism of action of the Crystalens (i.e., accommodation achieved by the forward and backward movement of the lens optic along the axis of the eye). Testing included dynamic retinoscopy, defocus, near point evaluation, near vision through the distance prescription with cycloplegia, power mapping with the [redacted], and anterior chamber depth measurement using A-scans following the administration of cyclopentolate and 6% pilocarpine.

Reviewer Comment: *In 1999 when the IDE for the parent IOL pivotal trial was first presented to the FDA and the clinical trial initiated, pseudophakic accommodation was a relatively new concept. At that time there were still no studies that had validated clinical methods to measure pseudophakic accommodation. In addition, at the time of the original Crystalens trial, FDA did not require such measurements to demonstrate accommodative amplitude.*

[redacted]

Reviewer Comments: *Of note, there were no control eyes for these accommodative substudies and the methodology was not validated.*

6.1.2. Initial Study of the Toric Accommodating IOL

A clinical investigation of a toric version of the PMA approved Crystalens Model AT-45 Accommodating Posterior Chamber IOL was originally initiated under an IDE supplement

[redacted]

[redacted]

Reviewer Comment: *Please be advised that none of the subjects from this earlier study are included in the PMA cohort.*

Reviewer Comments: *The subjects from the phase I study were not pooled with the subjects in the pivotal trial below.*

6.2. PMA Cohort Clinical Study – Pivotal Trial

6.2.1. Study Design/Overview

The objective of the trial (IDE supplement G990163/S049) was to demonstrate the safety and effectiveness of the toric modification of the Crystalens accommodating IOL (now known as the Trulign™ Toric Accommodating IOL). This was a multicenter, prospective, single-masked,

partially randomized/controlled, monocular study of 229 subjects conducted at 9 sites. Subjects were followed for up to 1 year with early termination permitted when IOL rotational stability was achieved. The primary endpoint was percent reduction in absolute cylinder expressed as a percentage of the intended reduction in cylinder at the Form 4 visit (4-6 months after surgery). The study included three Toric IOL models: AT-50T1 (1.25 D cylinder), AT-50T2 (2.00 D cylinder) and AT-50T3 (2.75 D cylinder). The AT-50T has a 5 mm optic and the overall length is 11.5 mm (loop tip to loop tip measurement).

Reviewer Comment: *Note that the Applicant chose to use a different lens model in this trial, the AT-50T, rather than the* [redacted].

The Toric Calculator software was used to determine which of three cylinder powers (1.25D, 2.00D, 2.75D) a given eye was eligible to receive. If an eye was eligible for implantation with the 1.25 D toric model, that eye was randomized to implantation with either the toric model or the spherical analog. (Eyes eligible for the other toric models were in a single arm study.) Only subjects in the lowest indicated corneal astigmatism range were to be masked to lens type implanted.

In this study, only monocular implantation of the toric accommodating IOL was permitted and the control device was the parent IOL (Crystalens Spherical Accommodating IOL). Some subjects did undergo implantation of the parent IOL (Crystalens Spherical Accommodating IOL) in the fellow (non-study) eye. The first subject was implanted on June 1, 2010 and the last subject was implanted on September 22, 2011. The last subject exited the study on September 10, 2012.

6.2.2. Eligibility Criteria

Please see Appendix A for a complete list of inclusion/exclusion criteria

6.2.1.1 Key Inclusion Criteria

Subjects ≥ 18 years with clinically documented diagnosis of age-related cataract (either cortical, nuclear, subcapsular, or a combination) that was considered amenable to treatment with standard phacoemulsification/extracapsular cataract extraction, who required a lens power from 16 to 27 D, and who had predicted postoperative corneal astigmatism between 0.83 D and 2.50 D as determined by the Toric Calculator were included.

6.2.1.2 Key Exclusion Criteria

Subjects who had any anterior segment pathology for which extracapsular/ phacoemulsification cataract surgery would have been contraindicated, diagnoses of degenerative visual disorders that were predicted to cause future acuity losses to a level of 20/32 or worse, conditions associated with increased risk of zonular rupture, could not achieve pupil dilation of 5.0 mm, and a difference in corneal astigmatism measured with the IOL Master and the topographer greater than 0.5 D using vector analysis were excluded.

6.2.3. Study Objective and Endpoints

As per the study protocol, the study objective was "to evaluate the safety and effectiveness of the Bausch + Lomb Toric Accommodating Posterior Chamber Silicone IOL Model AT-50T used to provide near, intermediate, and distance vision and a reduction of the effects of preoperative corneal astigmatism in subjects undergoing cataract extraction and IOL placement."

> ***Reviewer's Comments:*** *The study did not include outcome measures to assess accommodation.*

6.2.1.3 Primary Effectiveness Endpoints

Primary effectiveness endpoints included percent reduction in cylinder, expressed as a percentage of the intended reduction in cylinder:

$$\frac{\left(\left|\text{Postoperative Manifest Refractive Cylinder}\right| - \left|\text{Preoperative Keratometric Cylinder}\right|\right)}{\left(\left|\text{Intended Postoperative Manifest Refractive Cylinder}\right| - \left|\text{Preoperative Keratometric Cylinder}\right|\right)} * 100$$

Primary endpoints also included percent of eyes with "reduction of cylinder" within 0.50 D and within 1.00 D of intended and lens axis misalignment as determined by a photographic method. Effectiveness endpoints were evaluated at Form 4 (4-6 months postoperatively)

6.2.1.4 Secondary Effectiveness Endpoints

Secondary effectiveness endpoints include lens misalignment as determined by post-op manifest refraction and vector analysis, intermediate visual acuity with distance correction (DCIVA) at 32 inches (80 cm), near visual acuity with distance correction (DCNVA) at 16 inches (40 cm) (with and without the minimal reading add for the distance-corrected near visual acuity), best corrected distance visual acuity (BDCVA), and uncorrected distance (UCDVA), intermediate (UCIVA), and near visual acuity (UCNVA).

6.2.1.5 Other Effectiveness Endpoints

Other effectiveness endpoints that were to be analyzed, but not listed as endpoints included residual refractive cylinder, IOL rotation between visits (to help establish stability), and patient-reported visual disturbances evaluated by questionnaire.

6.2.1.6 Safety Endpoints

Safety endpoints included preservation of BCVA (distance and near) and incidence of complications and adverse events which will be compared to the ISO Safety and Performance Endpoints (SPE).

6.2.4. Statistical Analysis Plan

The planned sample sizes were 62 eyes for the toric IOL 1.25D arm and 65 eyes for the control. With these sample sizes, the study has a 90% power to detect a 34% difference in percent

reduction of cylinder with a 2-sided Type I error rate of 0.05. For arms of toric IOL with higher cylinder powers (2.00D and 2.75D), a total of 50 eyes were planned to provide descriptive results rather than statistical comparisons to the control.

The primary endpoint is percent reduction in absolute cylinder expressed as a percentage of the intended reduction in cylinder at the Form 4 visit (4-6 months after surgery). The null hypothesis is:

> H0: Percent reduction of cylinder in toric IOL 1.25D cohort≤ Percent reduction of cylinder in control cohort.

The alternative hypothesis is:

> H1: Percent reduction of cylinder in toric IOL 1.25D cohort > Percent reduction of cylinder in control cohort.

The hypothesis was tested using a two-sample, one-sided t-test with alpha error of 5% assuming unequal variances.

Secondary endpoints include 1) lens misalignment as determined by post-op manifest refraction and vector analysis; 2) intermediate visual acuity with distance correction at 32 inches (80 cm); 3) near visual acuity with distance correction at 16 inches (40 cm), with and without the minimal reading add for the distance-corrected near visual acuity; 4) best-corrected distance visual acuity; and 5) uncorrected distance, intermediate, and near visual acuity. There was not a planned formal comparison between the toric IOL cohorts and the control cohort for the secondary endpoints. Only descriptive statistics were to be presented.

Subgroup analyses were not planned in the protocol. Per the FDA's request, subgroup analyses by gender, age and investigators were conducted for the first primary endpoint (percentage of the intended reduction in cylinder).

Reviewer Comments: *Of note, on 3/17/2011 and 5/6/2011, two unplanned interim analyses were conducted before the statistical analysis plan was finalized. The Applicant's interim analyses were conducted after all patients had been enrolled. The sample size and patient selection were not affected by the interim analyses. However, there were changes in SAP after the interim analyses were performed which could potentially influence the results in secondary effectiveness endpoints and safety endpoints.*

6.2.5. Schedule of Study Visits and Methodology of Assessments

Please see Table 4 for a complete summary of assessments performed as part of this trial.

The study began with a screening and baseline exam prior to the operative procedure. During the surgery, the cataract was removed and the Trulign™ lens was implanted. The surgical procedure included the following relevant details:

- to prevent forward vaulting of the optic, an incision width of no greater than 3.0 mm for the AT-50T was recommended with a paracentesis of approximately 1.5 mm long, made using the surgeon's standard instrumentation and technique;
- incision was placed at the preoperative keratometric steep axis for all test and control eyes;
- decision regarding the cohesive viscoelastic was left to the surgeon's preference ;
- an anterior round capsulorhexis of 5.5 mm to 6.0 mm was made to allow the anterior capsule to cover the plate haptics while keeping the optic free, using the surgeon's standard technique;
- the cataract was extracted by phacoemulsification; sutures were not used to close the wound unless absolutely necessary as this could induce astigmatism;
- the AT-50T or AT-50SE was not implanted if there was a posterior or anterior capsular tear, or zonular rupture;
- no corneal or refractive procedures (such as limbal relaxing incisions or astigmatic keratotomies) were permitted at any time during the course of the study; a validated insertion device was to be used; and
- bilateral implantation with investigational lenses was not permitted.

Decisions regarding whether the incision would be clear corneal, limbal, or scleral were left up to the surgeon and the type of incision was recorded on the surgical case report form (CRF). The complete surgical procedure is listed in Appendix B.

The Investigator was allowed to use any medical treatment that was judged appropriate and beneficial to the subject. All medications that were considered necessary for the subject's welfare were allowed at the Investigator's discretion.

Follow-up visits occurred at the following time points: Form 1 on Postoperative Day 1-2, Form 2 on Postoperative Day 7-14, Form 3 on Postoperative Day 30-60, Form 4 on Postoperative Day 120-180, Form 5 on Postoperative Day 245-301, and Form 6 on Postoperative Day 330-420.

The misalignment of the toric IOL at Form 4 was assessed using an image analysis technique. Prior to insertion of the Toric IOL, reference markings were made to indicate the target axis for alignment. These reference markings were imaged and used to quantify the amount of misalignment at Form 4. Images at different time points were registered using iris features and conjunctival vessels to compensate for any eye rotation. A second assessment of IOL axis misalignment was performed by assuming that the captured image of the eye was horizontally oriented and then comparing the measured IOL axis orientation to the target axis

Distance visual acuities were assessed using the [redacted] (a "look in" device) and near and intermediate VAs were assessed using the MNRead card at 16 inches and 32 inches respectively.

Reviewer's Comments: *Of note, no objective measures of accommodation were included in this trial. However, FDA communicated our concern regarding the lack of accommodation measures via a PMA concern.*

6.3. Subject Accountability

A total of 9 sites (including one in Canada) enrolled 229 subjects; 158 subjects were randomized to toric IOL 1.25D and the Control arms and 71 subjects were enrolled to the 2.00 D and 2.75D Toric arm. 2 subjects discontinued before implantation due to surgical complications and 2 subjects discontinued after implantation (1 withdrew consent, 1 died).The PMA was submitted with 15 subjects still active.

Reviewer's Comments:
This executive summary is based on the analyses and FDA review of data presented in the original application through Amendment 4, which were based on interim data. However, on January 22, 2013, FDA received a final study report (Amendment 6) from the Applicant, which includes data and analyses through the completion of this study. This Amendment was submitted after the initiation of the writing of this executive summary and the data submitted are still under review. Therefore, there may be differences between the Applicant's executive summary/panel presentation and the data presented in FDA's executive summary/panel presentation.

A total of 229 subjects were included in the **All Enrolled Cohort**. The All Enrolled Cohort includes all subjects who were enrolled in the study regardless of whether they underwent cataract surgery. Subjects who were enrolled but discontinued prior to surgery were included in this cohort but not included in the **Safety Cohort**. Tables 5-7 show subject accountability analyses by visit and by IOL. A total of 229 subjects were included in the Safety Cohort. The Safety Cohort includes all subjects who underwent surgery for the implantation of a study lens (either test or control), whether a study lens was implanted or not. Subjects who were implanted were included in the Safety Cohort only if their lens was not repositioned. Safety measures were presented separately for study eyes implanted with the study lens and study eyes not implanted with the study lens. Study eyes that discontinued prior to attempting the surgery were excluded from all safety analyses. A total of 227 subjects were included in the Safety Cohort for implanted subjects, and 2 subjects were included in the Safety Cohort for subjects not implanted. A total of 215 subjects were included in the Effectiveness Cohort, as 14 subjects were excluded (i.e., 2 subjects were not implanted and 12 subjects had major protocol deviations). **The Effectiveness Cohort** includes all subjects who were implanted with a study lens (either Test or Control), whose lens was not repositioned, and who had no major protocol deviations. Protocol deviations were reviewed by Bausch + Lomb clinical personnel prior to analysis to identify subjects to be excluded from this Effectiveness Cohort. **The Repositioned Lens Cohort** includes all subjects who were implanted with a study lens (either test or control), whose lens was repositioned due to rotational misalignment; however, no subjects were included in the Repositioned Lens Cohort.

At the Form 4 visit, 229 subjects (100.0%) were accounted for, and 211 subjects (92.1%) were available for analysis. At Form 4, 3 subjects (1.3%) were discontinued, and 15 subjects (6.6%) were still active. At Form 4 there were 69 subjects available in the control arm (from the 76 enrolled), 74 subjects available in the Toric 1.25D arm (from the 82 enrolled), 46 subjects available in the Toric 2.00D arm (from the 47 enrolled), and 22 subjects available in the Toric 2.75D arm (from the 24 enrolled).

Reviewer's Comments: *Of note, there were ten subjects who were implanted with IOL models that were not approved for use in this trial (Models AT-52T and AT-52SE which have a 12.0 mm overall diameter). There were a total of 10 such devices implanted: 5 Toric 1.25 D (Model AT-52T) lenses, 1 Toric 2.75 D (Model AT-52T) lens, and 4 Control (Model AT-52SE) lenses.*

6.4. Demographics

Various baseline subject characteristics and demographic data were reported. In general, the baseline characteristics between the experimental and control arms for the randomized portion of the study were not significantly different, including age and gender. Enrollment per site varied between 9 and 68. Tables 8-10 contains demographic data and Table 11 reports the potential range of cylinder in subjects enrolled in each study arm.

6.5. Protocol Deviations

A total of 401 protocol deviations occurred in this study (391 protocol deviations were reported by the Applicant in addition to the ten unapproved lenses that were implanted during the study and identified as additional protocol deviations by FDA), 24 major protocol deviations (those impacting data analysis) and 377 minor protocol deviations were observed . (Note that the 24 major protocol deviations consist of 14 major protocol deviations identified by the Applicant and then ten unapproved lenses that were implanted during the study and identified as protocol deviations by FDA). See Table 12.

Reviewer Comments: *Due to Applicant's concerns regarding the deviations, study oversight was transferred from an external consultant to the Bausch + Lomb Clinical Operations group in September 2010, at which time approximately 80 subjects had undergone IOL implantation. Additional changes included appointment of an internal study manager to oversee clinical operations, increased monitoring resources, site retraining efforts and enhanced peer scientific oversight by internal clinical scientists and a consultant Medical Monitor. These improvements were implemented by the end of 2010 along with a protocol amendment that was implemented to clarify the study plan and correct errors and inconsistencies within the document.*

The types of major protocol deviations included the following: enrollment outside of eligibility criteria (BCVA eligibility criteria, chronic steroid use, amblyopia, incorrect keratometry values used with vector calculations), and implantation of study lens despite anterior/posterior capsular tear during surgery.

In addition to the deviations listed above, ten subjects were implanted with IOL models that were not approved for use in this trial (Models AT-52T and AT-52SE which have a 12.0 mm overall diameter). There were a total of 10 such devices implanted: 6 toric AT-52T lenses and 4 spherical AT-52SE lenses.

Reviewers' Comments: *The Applicant included these subjects with the original PMA submission, but were informed in a major deficiency letter that FDA considers implantation of these lenses to be protocol deviations and requested that these subjects be excluded from the effectiveness analyses. The Applicant complied with this request.*

Minor deviations include out of window visits, consent process deviations, visual acuity (VA) measurements not done (or performed with different methodology than described in the protocol), surgical video or post op photos not captured, or site completion of the Subject Questionnaire Case Report Forms (CFRs) for the subjects (or complete CRF using subject completed source).

Among the minor deviations, there were 77 protocol deviations reported specifically as Visual acuity (VA) measurements (best-corrected visual acuity [BCVA], uncorrected visual acuity [UCVA- Intermediate, or Near]) not done, [redacted] not used or MN card not used. In total, there were 77 protocol deviations reported in this category. The majority of these deviations (74/77) involved VAs obtained between the preoperative and Form 3 visits, and the remaining 3/77 deviations occurred at the Form 4 visit.

Also among the minor deviations, 39 deviations were classified as "Surgical video or post op photos not captured". According to the study protocol, a video of the cataract surgery was to be recorded. In addition, a digital photograph of the implanted eye was also to be taken immediately after surgery. The majority (26/39) of these deviations occurred at the operative visit with 25 being the absence of surgical video and one the absence of a digital photograph.

The remaining 13/39 deviations in this category were related to the digital photographs at Forms 3 and 4. Deviations were reported for missing Form 3 digital photographs (n= 10 subjects) at the time of interim analysis timepoint. At the Form 4 visit, 2 subjects were reported as having missing photographs and 1 subject was reported to have an unusable photograph. Therefore, these subjects were excluded from the interim analysis as only eyes with usable, non-missing images at both Form 3 and Form 4 were included in the analysis of rotational stability.

Finally, some minor deviations were listed as "Site completed the Subject Questionnaire Case Report Forms (CRFs) for the subjects, or complete CRF using subject completed source." For example, during initial monitoring visits conducted at two sites, it was identified that subjects were not recording their responses directly on the paper CRF provided by the Applicant. At one site, eleven subjects were provided source worksheets of the questionnaires to complete. The study coordinator then transcribed the information from the source worksheets onto the CRFs submitted to the Applicant. At another site, the study coordinator read the questions to 19 subjects and recorded answers directly onto the CRF. The CRF questionnaire pages provided to the study sites had the statement "To be administered by Physician or Designee" on each page. The study protocol specified that the subject was to complete the questionnaire; therefore, these conditions were categorized as protocol deviations.

The study had 401 protocol deviations, of which 24 were considered major. The panel will be asked to consider whether, given the over 400 protocol deviations (ranging in severity from implantation of a device model which was not approved for the study to out of window visits), they believe that the design and conduct of the study used to support the Trulign™ Toric Accommodating IOL are able to demonstrate that the benefit from the use of the device outweighs the risk.

7. Clinical Study Results

7.1. Safety Endpoints

7.1.1. Analysis Population

The analysis population for the safety endpoints is the Safety Cohort. The Safety Cohort includes all subjects who underwent surgery for the implantation of a study lens (either test or control), whether a study lens was implanted or not. Subjects who were implanted were included in the Safety Cohort only if their lens was not repositioned. Safety measures were presented separately for study eyes implanted with the study lens and study eyes not implanted with the study lens. Study eyes that discontinued prior to attempting the surgery were excluded from all safety analyses. A total of 227 subjects were included in the Safety Cohort for implanted subjects, and 2 subjects were included in the Safety Cohort for subjects not implanted.
Of the 229 subjects, 76 were in the control arm, 82 were in the Toric IOL 1.25D arm, 47 were in the Toric IOL 2.00D arm, and 24 were in the Toric IOL 2.75D arm.

7.1.2. Preservation of BCVA (distance and near)

Best-Corrected Distance Visual Acuity (BCDVA) was evaluated both by the percentage of subjects reporting a BCDVA of 20/40 or better and the percentage of subjects experiencing a decrease in BCDVA of 10 letters or more. See Tables 13-14. BCDVA of 20/40 or better was reported for 143 eyes (99.3%) and 139 eyes (97.9%) at the Form 3 and Form 4 visits, respectively. Of eyes experiencing a decrease in BCDVA of 10 letters or more, etiologies included dry eye, posterior capsular opacification, corneal edema, or unexplained losses which resolved at a later visit. Table 15 summarizes the preservation Best-Corrected Near Visual Acuity (BCNVA)at each visit. BCNVA of 20/40 or better was reported for 141 eyes (98.6%) and 142 eyes (100.0%) at the Form 3 and Form 4 visits, respectively.

7.1.3. Complications and Adverse Events

Adverse events (AEs) are compared to the ISO Safety and Performance Endpoints (SPE). Cumulative AEs reported for the Safety Cohort were those AEs which occurred at any time through Form 4. Persistent AEs were defined as present at Form 6. Tables 16-17 display the rates of cumulative and persistent AEs reported for the Control and All Toric cohorts, as compared to the ISO SPE. Of the 76 eyes in the Control cohort, 1 cumulative AE (1.3%) of macular edema and 1 cumulative AE (1.3%) of secondary surgical intervention were reported through Form 4. Of the 151 eyes in the All Toric cohort, 1 cumulative AE (0.7%) of macular edema and 1 cumulative AE (0.7%) of secondary surgical intervention were reported through the Form 4 visit.

The two cases of secondary surgical intervention consisted of lens repositioning not related to lens axis misalignment or rotation. One eye in the Control cohort experienced lens malposition at postoperative day one. The second eye in the Toric 2.00D cohort experienced lens vaulting at the Form 4 visit.

Reviewer Comment: *Anterior vaulting will be discussed in detail below in section 7.1.5.1.*

The rate of reported macular edema (2/227, 0.9%) is below the ISO SPE rate (3.0%) and PMA P030002 (3.7%). The rate of reported secondary surgical intervention (2/227, 0.9%) is slightly higher than the rate reported in the ISO SPE (0.8%) and the PMA for the parent IOL from P030002 (0.6%).

The ISO SPE proportions for cumulative AEs are: endophthalmitis (0.1%), hypopyon (0.3%), lens dislocated from posterior chamber (0.1%), macular edema (3.0%), pupillary block (0.1%), retinal detachment (0.3%), and secondary surgical intervention (0.8%). For persistent AEs, the proportions are as follows: macular edema (0.5%), corneal edema (0.3%), iritis (0.3%), and raised IOP requiring treatment (0.4%).

Reviewer Comment: *Please note the toric arm did not exceed the ISO SPE rate for any type of AE. The control arm did exceed the ISO SPE rate on secondary surgical interventions*

Surgical AEs are listed in Table 18. A total of 10 surgical AEs were reported during this study. Of those, 7 Implanted Subjects experienced at least one surgical AE, and 2 Not Implanted Subjects experienced surgical AEs in the Safety Cohort (both were randomized to the toric 1.25D lens for implantation: 1 case of capsulorhexis tear and 1 case of posterior capsule rupture, neither considered device-related). Of the Implanted Subjects experiencing surgical AEs, 2 subjects (2.6%) were in the Control cohort and 5 subjects (3.3%) were in the All Toric IOL cohort. Six AEs were judged by the Investigator to be related to the study procedure, and severity was assessed as mild in all cases.

All ocular AEs occurring in the Study Eye reported through Form 4 of the Safety Cohort were reported.

Reviewer Comment: *In general, the non-SPE ocular adverse events show rates to be similar in the toric and non-toric lenses.*

Non-Ocular Adverse Events were discussed in the submission. None appear to be device related.

7.1.4. Other Safety Cohort Analyses

Tabulations of IOP changes over time, biomicroscopy findings, posterior capsular opacification, and ND:YAG capsulotomies were also performed.

Reviewer Comment: *In general, the "other safety cohort analyses" show rates to be similar in the toric and non-toric lenses.*

7.1.5. Serious Adverse Events

Eleven reports of serious adverse events (SAEs) in 11 subjects were identified from the initiation of the trial through the Form 4 visit.

Eight of the 11 were non-ocular events that were all assessed by the Applicant to be unrelated to the study device and procedure: death, transient ischemic attack, aspergillosis, renal artery block, cystitis, right knee sarcoma, unspecific cardiac event), and B-cell lymphoma of the fellow eye.

Three of the 11 reported events were related to an ocular finding. One subject experienced an IOL malposition of the Control device that was assessed by the Investigator to be possibly related to the study procedure. The second experienced an anterior vault of the 2.00D Toric IOL that was assessed by the Applicant to be probably related to the study device and possibly related to the study procedure. The third occurred in a fellow eye and experienced an anterior vault that was assessed by the Applicant to be unrelated to the study device or procedure.

Reviewer's Comment: *Please note that there were two cases of anterior vault which occurred during the course of this study. One event occurred in an eye receiving the toric 2.00D IOL and one occurred in a fellow of a subject enrolled in the toric 1.25D arm who received the IOL outside of the study. The fellow eye was not enrolled in the study, and the event involved a different model Crystalens IOL. Aside from the cases of anterior vaulting, further discussed in 7.2.5.1, the serious adverse events rates are similar for the toric and non-toric lenses.*

7.1.5.1. Anterior Vaulting

The Crystalens is designed to vault forward with ciliary muscle contraction when focusing at near and return to its original position with ciliary muscle relaxation when focusing at distance. The "anterior vault" listed as an adverse event does not refer to this expected movement of the Crystalens, but rather to the condition that occurs when the lens optic becomes lodged in an anterior position independent of ciliary muscle relaxation or contraction, that is, whether the patient is focused at distance or at near. Furthermore, the Applicant has reported that an asymmetric combination of capsular contraction forces and vitreous pressure can result in the anterior vault of one hinge and the posterior vault of the other hinge. This creates an asymmetric tilt of the Crystalens, known as Z-Syndrome. This adverse event can result in the need for secondary surgical interventions.

Reviewer Comment: *Anterior vault was identified as a potential adverse event at the time of approval of the parent IOL; however, there was one case of explantation due to vault in the original pivotal study with 324 subjects and 497 eyes. Subsequent to the PMA approval, there were additional cases of anterior vaulting. This prompted the Applicant to submit a supplement to the PMA (Supplement 5) requesting labeling changes in order to mitigate this issue. The labeling revisions addressed the need for a larger capsulorhexis size than previously recommended (5.5 to 6.0 mm rather than 5.0 mm to 5.5 mm), recommendation that meticulous cortical clean-up should be performed and the lens rotated at least 90° to dislodge any hidden or trapped cortex, and recommendation that patients should be kept on a tapering course of anti-inflammatory agents for a minimum of 4 weeks. Supplement 5 was approved on September 26, 2005. Subsequently, there were additional minor labeling revisions made related to mitigating potential vaulting issues.*

There were two cases of anterior vault of the Crystalens in study subjects of this PMA Cohort. One of the two cases did not occur in a study eye, but rather in the fellow eye which underwent

implantation with the parent Crystalens IOL. Both cases were identified at the form 4 visit (4-6 months postoperatively). One case was attributed to possible noncompliance with medications. The other was thought to be associated with zonular dehiscence and capsular contraction causing the lens to asymmetrically vault. Case summaries are included in Appendix C.

Reviewer Comment: *It is unclear when noncompliance occurred and why noncompliance with medications would be an issue 4-6 months postoperatively resulting in anterior vault , It is also unclear at what point zonular instability developed in the other case. The subject initially underwent lens repositioning due to anterior vault of the Crystalens IOL, then implantation of another Crystalens IOL was attempted, however this lens also vaulted. Subsequently, zonular instability was discovered.*

7.1.5.1.1. Applicant's Analyses of Anterior Vaulting

As a result of the reports of anterior vault in the current study, FDA requested that the Applicant provide additional detail concerning the description and diagnoses of these events, a full discussion of the incidence, timing (e.g., time after implantation), diagnosis, treatment, and probable causes of this type of problem based upon the Applicant's experience with all Crystalens models including an examination and report concerning complaints filed either in the U.S. or internationally, and any such reports (published or unpublished) of which they are aware since the lens platform for the proposed IOL is identical to that of the parent.

The Applicant has reported that this adverse event can be associated with either patient or procedure related factors. The Applicant identifies the following reported patient related factors: non-compliance with postoperative prescribed medications (note that the directions for use for the parent IOL was revised to state patients should be kept on a tapering course of anti-inflammatory agents for a minimum of 4 weeks), capsular contraction syndrome caused by a rare aggressive healing response, or zonular laxity. The Applicant identifies the following reported procedure related factors, which have been addressed in labeling revisions to the parent IOL. These include incisional wound leak, failure to remove all lens material during surgery (lens should be rotated at least 90 degrees to dislodge any hidden or trapped cortex), inadequate or irregular capsulorhexis (smaller than 5.5-6.0 mm or anterior capsule unable to cover plate haptics), zonular damage and failure to provide cycloplegic medication.

As requested by FDA, the Applicant searched their global database and reported: "The total number of specific complaints for Z-Syndrome reported between [redacted]. The total number of implanted Crystalens IOLs during that same time is [redacted]. "Information regarding model type was provided for [redacted]

[redacted]

[redacted]

7.1.5.1.2. Results of FDA search of the Manufacturer and User Facility Device Experience Database

In addition to the adverse event information that was provided by the Applicant, a search of the Manufacturer and User Facility Device Experience (MAUDE) Database was conducted by FDA to investigate anterior vaulting related to Crystalens IOL (See Appendix D for full analysis). Appropriate interpretation of MAUDE data requires understanding of its strengths and limitations. First, although Medical Device Reports (MDRs) provide important postmarket data related to the experience of device users, it is not appropriate to attempt to determine the rate or frequency of particular events based on MDRs, due to reporting bias and the lack of denominator data. Second, the quality and quantity of information included in an MDR varies greatly between MDRs, often providing little context for an adverse event and subsequently limiting data interpretation. Furthermore, the presence of an MDR does not definitively establish causality between the device issue and the adverse outcome. This preliminary analysis of MDRs associated with the Crystalens IOL should be interpreted within the constraints of these limitations.

The MAUDE database was searched on January 25, 2013 using the following search terms: All variations of ”crystalen” (35 variations) prior to January 25, 2013. Please note, changing the search parameters may yield a different number of reports. A total of 1,268 MDRs, including 1,106 Injury reports and 162 Malfunction reports, reported for the Crystalens IOL were identified. These reports represent 10 years of reporting history between 2004 and2013. To identify reports of specific clinical issues possibly related to anterior vaulting, the text was searched using the following terms : tilt, fibrosis, position, location, locate, contract, remove, vaulting, vaulted, malpositioned device, positioning issue, dislodge, dislocated, explanted, explant, exchange, vault, capsular contraction syndrome, CCS, phimosis, removed, malposition, tilted, and z-syndrome. The text search revealed a total of 875 MDRs, including 835 Injury reports and 40 Malfunction reports.

Device and patient problem data is reported to the FDA by the manufacturer in the form of Device and Patient Problem Codes. Please note these Device and Patient Problem Codes are based on the manufacturer’s analysis of the adverse event, and are not derived by FDA. Additionally, multiple Device and Patient Problem Codes may be reported in each adverse event

report, and therefore the total number of problem codes may exceed the number of MDRs. Preliminary analysis of Device and Patient Problem Codes using online analysis tools within the MAUDE database was completed to identify frequently reported device and patient problems reported for the Crystalens IOL.

Based on a preliminary analysis of Device and Patient Problem Codes for the results of the text search, procedural and device-related events included MDRs reporting Haptic broken (N= 221), Haptic damage in delivery system (N=206), Lens damaged in delivery system (N=87), Malposition of device (N=86), Lens torn, split, cracked (N=78), and Lens vaulting (N=76). Clinical outcome events included reports of Lens replacement (N=459), Surgical incision enlargement (N=311), Capsular bag tear (N=115), Capsular contracture (N=76) and Vision impairment (N=56).

7.1.5.1.3. FDA's Literature search

FDA also conducted a systematic literature review to assess the issue of anterior vault related to the Crystalens Accommodating IOL. After application of exclusion and inclusion criteria, 9 articles were included in this review. Of the 9 papers that were reviewed, two were meta-analyses, 3 case reports, 2 case series and 2 longitudinal cohort studies. When evaluating the literature, FDA determined that there was limited discussion in the literature related to the issue of anterior vault. There are only three case reports with a total of four subjects experiencing severe lens tilt, or vault change, or z-syndrome caused by capsular fibrosis. In the reports, these problems were remediated with neodymium:YAG (Nd:YAG) laser or surgical replacement of the accommodative IOL with monofocal IOL. The detailed review by the Division of Epidemiology with references is provided in Appendix E.

Given two reports of anterior vault in the current clinical study and the information available regarding the incidence of this adverse event in the parent IOL (from MDR's, published literature, and the global complaints and adverse events reported to the Applicant, etc.), the panel will be asked if the incidence of anterior vaulting and capsular contraction syndrome raise a significant safety concern with respect to the risk of this adverse event in implanted eyes for the subject device.

7.2. Effectiveness

7.2.1. Analysis Population

The Effectiveness Set included all subjects who were implanted with a study lens (either test or control), whose lens was not repositioned, and who had no major protocol deviations. Subjects whose lens was repositioned were excluded from all primary safety and effectiveness cohorts, and data for these subjects were analyzed separately from the primary cohorts.

There were 215 subjects (215 eyes) analyzed in the Effectiveness Cohort [73 Control, 142 toric (77 in the 1.25 D, 41 in the 2.00 D, and 24 in the 2.75 D)]. Of those, 174 subjects were analyzed in the Best Case Cohort (no clinically significant preoperative ocular pathology), 41 subjects

were analyzed in the Not Best Case Cohort, and 121 subjects from the All Toric cohort were analyzed in the Consistent Cohort (subjects available at all postoperative visits from Form 3).

7.2.2. Primary Effectiveness Endpoints

A 2-sample, 1-sided t-test assuming unequal variance was performed using the Effectiveness Cohort to test the null hypothesis that the percent reduction of cylinder within the eyes implanted with IOL cylinder power 1.25 D was less than or equal to the percent reduction of cylinder within the eyes implanted with the Control IOL.

The mean percent reduction in cylinder at Form 4, expressed as a percentage of the intended reduction in cylinder is described by the following equation:

$$\frac{\left(\left|\text{Postoperative Manifest Refractive Cylinder}\right| - \left|\text{Preoperative Keratometric Cylinder}\right|\right)}{\left(\left|\text{Intended Postoperative Manifest Refractive Cylinder}\right| - \left|\text{Preoperative Keratometric Cylinder}\right|\right)} * 100$$

In addition, the intended reduction in cylinder consisted of the 0.50 D incisional effect added to the IOL cylinder power in the corneal plane. (Note that the "intended reduction in cylinder" was the same for both arms of the randomized group, even though the control eyes were not receiving the toric IOL.) In the randomized portion of trial, the Toric Arm (1.25 D) showed a percent reduction of 81% and the Control Arm demonstrated a percent reduction of 46%. Thus, the treatment effect is approximately 35%. This is statistically significant at $p < 0.0001$. In the toric 2.00 D arm, the percent reduction was 88%. In the toric 2.75 D arm, the percent reduction was 97%. Results appear in Table 19.

Reviewer Comment: *Note that the calculations of the toric calculator assume that the incision will have an effect of 0.50 D reduction. Inclusion Criterion #6 requires predicted postoperative corneal astigmatism of at least 0.83 D. So for all patients in the randomized portion of the study, the preoperative corneal astigmatism would always have to be at least 0.83 + 0.50 D or 1.33 D. For this IOL power (1.25 D), there was never any planned overcorrection. For toric-implanted eyes in the randomized portion of the study, the intended postoperative manifest refractive astigmatism would always be due to an under-correction (from 0 to 0.49 D based on the preoperative corneal cylinder). For the toric and control eyes in the randomized portion of the study, the intended reduction in cylinder was always 1.33 D (0.83 D + 0.50 D) – thus, this effectiveness measure includes the effectiveness of the incision in reducing cylinder. For small cylindrical corrections this is a significant proportion of the percent reduction. Comparison to the control helps to reduce this concern. The fact that the control achieved a percent reduction of 46% should be considered in the context of the incisional effect. If the incision did have an effect of 0.50 D, this would yield approximately a 38% reduction in absolute cylinder (0.5/1.33). See Table 20 for toric IOL cylinder powers and selection criteria.*

Analysis of the percent reduction in cylinder indicates that the treatment effect (difference between control and toric arms) in the randomized portion of the study is greatly affected by the age of the subject as demonstrated in Table 21. In older patient groups (age ≥ 60), the percent reduction in cylinder is higher in the toric arm than that in the control arm. In the younger patient group with age < 60, the percent reduction in cylinder is lower in the toric arm than that in the

control arm. The difference in treatment effect between older and younger patients results in a treatment by age interaction with $p < 0.01$.

For the randomized portion of the study, statistical analysis indicates decreasing difference between test and control arms, in terms of reduction of cylinder, with decreasing age. Below age 60, the control arm had greater percent reduction in cylinder than the toric arm. The panel will be asked to discuss this issue including:

- ***a. Probable causes;***
- ***b. How this influences study conclusions;***
- ***c. Any recommendations you may have concerning mitigation of this problem through limitations to the Indication for Use; and***
- ***d. Any recommendations you may have concerning mitigation of this problem through labeling changes***

The observed treatment effect of toric IOL 1.25D cohort vs. control cohort is higher in the male group than that in the female group (46.7% in male and 25.2% in female) as shown in Table 22. The observed difference in treatment effect between male and female is also statistically significant with p=0.1.

Analysis of the percentage of eyes with "reduction of cylinder" within 0.50 D and within 1.00 D of intended demonstrated the following: In the randomized portion of the study, 82% of the subjects implanted with the Toric 1.25D were within 0.50D of intended cylinder and 46% of the control arm. In the Toric 2.00 D arm, 80% of the subjects were within 0.50D. In the Toric 2.75 D, 73% of subjects were within 0.50D. In the randomized portion of the study, 96% of the subjects implanted with the Toric 1.25D were within 0.50D of intended cylinder and 73% of the control arm. In the Toric 2.00 D arm, 93% of the subjects were within 0.50D. In the Toric 2.75 D, 100% of subjects were within 0.50D. See Table 23.

Lens Axis Misalignment as determined by a photographic method was measured relative to both Surgical Markings and Target Axis. For both, the absolute value and the signed values of lens axis misalignment are presented in degrees. The absolute value of lens axis misalignment from the Surgical Markings by direct measurement for the Effectiveness Cohort at the Form 4 visit is presented in Table 24. Mean (SD) lens axis misalignments of 2.594º (2.578º) for the 1.25 Toric Cohort, 2.144º (1.988º) for the 2.00 Toric Cohort, and 3.243º (2.729º) for the 2.75 Toric Cohort were reported. The majority of subjects (85.5% in the 1.25 Toric Cohort, 86.5% in the 2.00 Toric Cohort and 80.0% in the 2.75 Toric Cohort) reported less than 5° lens axis misalignment. 97.6% of subjects in the All Toric Cohort reported an axis misalignment of less than 10° and no (0%) subjects reported an axis misalignment of greater than 30°. See Tables 24-27. Misalignment from target compares the observed lens axis angle to the target angle provided by the toric calculator. In the absence of an objective target in the photographs (such as the surgical markings), the calculation of this endpoint assumes a vertical head orientation, on average, at the postoperative

visits. Theoretically, a vertical head orientation would be the position of the head during preoperative keratometry, when the biometric data used to establish the target lens axis orientation were obtained. Consequently, postoperative deviations between preoperative and postoperative head orientation could potentially have an effect on the magnitude and direction of this outcome and could result in a higher degree of perceived misalignment compared to measurement of lens misalignment from actual surgical markings.

7.2.3. Secondary Effectiveness Endpoints

7.2.3.1. Uncorrected distance (UCDVA), intermediate (UCIVA), and near visual acuity (UCNVA) at Form 4

Tables 28 - 31 provide these outcomes. Uncorrected acuities are highly influenced by the manifest refraction spherical equivalent (MRSE). For the randomized eyes (eligible for the 1.25 D toric implant), the differences between arms for mean uncorrected acuities statistically adjusted for MRSE (Tables 32 - 34) were as follows:

- UCDVA: 0.069 (p = 0.004) [better acuity in the toric arm]
- UCIVA: 0.037(p = 0.053) [better acuity in the toric arm]
- UCNVA: 0.018 (p = 0.403) [better acuity in the toric arm]

Reviewer Comment: *For randomized eyes, the mean uncorrected distance acuities showed a benefit of two thirds of 1 line for the toric arm compared to the control arm. However, at intermediate and near, the toric arm showed virtually no benefit compared to the control arm (0 to 2 letters). While a statistically significant difference between the two randomized arms was demonstrated on UCDVA, it was not demonstrated on UCIVA or UCNVA.*

The Applicant was asked to address these results and the following information was included in their response regarding the limited UCNVA improvement in the toric arm compared to the control:

> The accommodative amplitude for the Crystalens is approximately 1.00 D (per labeling). This is less than the full reading add of 2.50 D required to achieve optimal visual acuity at near. It is known that uncorrected astigmatism provides a degree of multifocality and can improve uncorrected near acuities. Thus, the control group (without astigmatism correction from the IOL) would be expected to get some benefit in uncorrected near acuity from this uncorrected astigmatism, and the full visual benefit of the toric correction would not be apparent from a comparison of these near acuities.

The proposed indications for use states the Trulign™ Toric Accommodating IOL is "intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia, who desire improved uncorrected distance vision and reduction of residual refractive cylinder. Trulign™ Toric provides approximately one diopter of monocular accommodation which allows for near, intermediate and distance vision without spectacles." The results from the study include uncorrected visual acuity data at 4-6 months

postoperatively (Form 4) demonstrating 0 to 2 letters of improvement for near vision in the toric arm compared to the control (spherical) arm. The same difference is seen in the two arms of the study with regard to the uncorrected intermediate visual acuities at 4-6 months postoperatively. Given the lack of significant improvement in the uncorrected near and intermediate acuities between the experimental and control arms, the panel will be asked if the data presented is sufficient to support the effectiveness of the device in light of the proposed indications for use.

7.2.3.2. Lens misalignment as determined by post-op manifest refraction and vector analysis

While this was listed as a secondary endpoint, the Applicant argued that this method is not productive as a measure of lens axis misalignment and did not provide the analyses. FDA has accepted the justification provided.

7.2.3.3. Intermediate visual acuity with distance correction (DCIVA) at 32 inches (80 cm)

DCIVA at 32 inches (80 cm) for the Effectiveness Cohort at the Form 4 visit was presented. The mean (SD) logMAR DCIVA was 0.090 (0.125) for the Control Cohort and 0.071 (0.111) for the All Toric Cohort. No statistically significant difference was found between the Control and All Toric Cohorts (p = 0.665)." There were similar acuities for the other cylinder-implanted groups. See Table 35.

7.2.3.4. Near visual acuity with distance correction (DCNVA) at 16 inches (40 cm), with and without the minimal reading add for the distance-corrected near visual acuity

DCNVA at 16 inches (40 cm) for the Effectiveness Cohort at the Form 4 visit was presented. The mean (SD) logMAR DCNVA was 0.305 (0.138) for the Control Cohort and 0.300 (0.144) for the All Toric Cohort. No statistically significant difference was found between the Control and Toric lens Cohorts (p = 0.912)." There were similar acuities for the other cylinder-implanted groups. See Table 36.

Reviewer Comment: *Note that near acuities were not compared to a "non-accommodating" IOL, just to the parent accommodating IOL.*

7.2.3.5. Best corrected distance visual acuity (BCDVA)

The submission provides comparisons for the rate of BCDVA achieving better than or equal to 20/40. In the effectiveness cohort at Form 4, subjects implanted with the toric accommodating IOL, 99% achieved a BCDVA greater than or equal to 20/40. For the safety cohort at the same timepoint, 97.9% achieved this outcome. See Tables 37 - 39.

7.2.4. Other Effectiveness Endpoints

Additional effectiveness endpoints include residual refractive cylinder, IOL rotation between visits (to help establish stability), visual disturbance questionnaire.

7.2.5. Residual Refractive Cylinder

In the randomized portion of the study, the subjects implanted with the toric (1.25 D) model demonstrated a mean residual cylinder of 0.5 D compared to 0.9D in the control arm. This is a treatment effect of about 0.4 D, which is statistically significant ($p < .001$). Other toric powers had similar residual refractive cylinder as the 1.25 D model at Form 4.

7.2.6. IOL rotation between visits

Axial rotation between visits was based upon analysis of the captured images. Rotational stability for all eyes attending the two consecutive visits reported at the Form 4 visit is presented in Table 40. Mean (±SD) axial rotation between Form 3 and Form 4 was 1.22 (±1.09) degrees. Ninety-nine percent of eyes (120/121 with measurements at both visits) had axial rotation ≤ 5 degrees between these two visits. (Rotational stability between consecutive visits for the Consistent Cohort reported at the Form 4 visit is presented in Table 41.)

7.2.7. Visual Disturbances Questionnaire

With regard to visual disturbances evaluated by questionnaire, five subjects (7.8%) in the Control Cohort and only a single subject (0.8%) in the All Toric IOL Cohort, experienced one or more significant visual disturbances. The one subject [redacted]) in the Toric Cohort with a significant visual disturbance was implanted with a 2.00 D Toric lens that was 1.23 degrees from its target axis orientation at the Form 4 visit. At this visit, the subject had developed moderate posterior capsule opacification (PCO). At the visit following Nd:YAG treatment, the subject reported via the questionnaire that the visual disturbances were resolved. No eyes in the highest cylinder correction reported significant visual disturbances.

7.2.8. Surgically Induced Astigmatism and the Toric Calculator

As noted previously, the protocol called for all corneal incisions to be placed at the steepest corneal meridian. For this study, it was assumed that the incision always had an effect of reducing corneal toricity by 0.50 D and never had any effect on keratometric axis. The 0.50 D was considered part of the "intended correction."

The Applicant-developed Toric Calculator software provided the predicted postoperative corneal cylinder power and axis, based upon the preoperative keratometric measurements and the assumed 0.50 D incisional effect. It should be noted that for the lower IOL powers, this incisional effect is a significant proportion of the intended correction. For the lowest toric cylinder power in the study, this incisional effect was 38% (0.50/1.33) of the intended correction.

The degree of effectiveness of the toric IOL astigmatic correction can be significantly dependent upon the accuracy of the Toric Calculator prediction.

The actual effects of the incision upon the corneal shape were analyzed based upon pre and postoperative keratometric data. Vector analysis was used to calculate the surgically-induced astigmatism (SIA) for the Effectiveness Cohort at Form 4. SIA is defined as the vector difference between the baseline and postoperative keratometric astigmatism vectors. The mean (SD) SIA was reported as 0.696 D (0.467 D) in the Control Cohort and 0.748 D (0.492 D) in the All Toric Cohort. See Table 42.

The accuracy of the Toric Calculator predictions were also analyzed. See Tables 43-44. Mean absolute differences were large enough to have substantial effects upon percent reduction for the randomized eyes (i.e., those requiring lowest toric cylinder power). The mean absolute error in the magnitude of cylinder was 0.34 D (26% of intended reduction for lowest power). Mean absolute error in the predicted axis was 11°. Absolute error in axis tended to be somewhat larger for low preoperative corneal toricities (Figure 2).

Reviewer Comment: *These data indicate the uncertainty in predicting the postoperative corneal toricity. Maximum surgically induced astigmatism was about 3 diopters, and the minimum was close to zero. About 7% of eyes in the randomized group had an error in the axis prediction of > 30 degrees, which translates to reducing the effectiveness of the IOL cylindrical effect to nothing. The dioptric reduction in cylinder is reduced approximately 3% for each degree of misalignment, so 11 degrees translates into a 33% reduction in effectiveness. (A significant proportion of the prediction error is likely related to keratometric measurement imprecision.)*

7.2.9. Accommodative amplitude of Trulign™ Toric Accommodating IOL

While no data on accommodative ability was collected as part of the study to support approval of the Trulign™ Toric Accommodating IOL, the lens design is built upon the same platform as the parent IOL; therefore, the accommodative ability is believed to be comparable.

Since the approval of the parent IOL, there has been much discussion in the published literature about the true accommodative ability of this lens platform. This is because of the limited data regarding accommodative amplitude that was presented for the parent IOL approval. In addition, there have been significant improvements in the methods for measuring accommodative amplitude since the approval of the parent Crystalens IOL.

The Crystalens was designed to move forward along the axis of the eye in response to contraction of the ciliary muscle (accommodative effort). However, the Applicant acknowledges that the exact mechanism of action has not been fully elucidated. It has been proposed that part of the mechanism of action of the Crystalens is not due to a true overall focal shift, but to increased aberrations or astigmatism (from tilt) related to ciliary muscle contraction (Dell SJ. Pilocarpine-induced shift of an accommodating IOL. J Cataract Refract Surg. 2005 Aug;31(8):1469-72; author reply 1472-5.).

Reviewer Comment: *Of note, this alternate mechanism of action does not represent true accommodation, but rather a variable depth of focus.*

The clinical trial for the approval of the parent Crystalens found evidence for improved levels of intermediate and near acuity, compared to a standard monofocal lens. However, it is well known that improved near acuity does not necessarily indicate functional accommodation. Acuity can be influenced by multiple non-specific factors including blur interpretation, corneal multifocality, depth of focus related to lens aberrations and pupil size. Some of these factors can be influenced by patient expectations and can play into a placebo effect. There has been some controversy within the ophthalmic literature as to whether the Crystalens actually provides significant true accommodation.

FDA conducted a systematic literature review to assess the issue of accommodation related to the Crystalens Accommodating IOL by searching and evaluating the existing clinical literature (See Appendix F for complete literature review and references). After application of exclusion and inclusion criteria, only ten English articles discussed measurement of the amplitude of accommodation with a Crystalens model. Articles that assessed near acuities, but did not attempt to measure amplitude of accommodation were not included in the analysis. Studies examining only subjectively measured accommodative amplitude of the Crystalens HD model were also excluded[2,3,4]. This is because the HD model uses a unique optical design that complicates the subjective accommodation assessment.[5] The seven remaining articles all used methods to objectively assess accommodation and three of these also used subjective measures. We note that subjective methods are subject to the same limitations as acuity measurements (e.g., impacted by subject effort and investigator interpretation/encouragement). See Appendix F for a summary of the seven articles.

Reviewer Comment: *The studies in the 7 articles varied in size and quality, with only 3 using control groups. Some articles used multiple measures of accommodation in their studies.*

There were 4 studies[6,7,8,9] which measured changes in anterior chamber depth (ACD) in response to accommodative stimulus. The mean changes in ACD in these studies varied from negative accommodative movement (deepening of the ACD) to positive accommodative movement (up to 0.3 mm). The 3 studies[5, 9,10] using aberrometry or refractometry measured mean amplitudes which demonstrated low (up to +0.45 D) to negative levels of accommodation. The single study[11] using dynamic retinoscopy (subjective on the part of the retinoscopist) found a mean amplitude of 2.4D. The 2 controlled studies using subjective measures of accommodation[6,11] found differences between test and control eyes of -0.2 D (i.e., control better) and +1 D (i.e., Crystalens better).

There were no objective measures of accommodation for the device captured in this study. Since approval, some studies from the published literature have demonstrated a lack of significant accommodative ability with the parent IOL while others support the accommodative ability of the parent IOL. The panel will be asked if the data presented are sufficient to support an accommodation claim for this device.

8. Post Approval Study (PAS)

Note: The inclusion of Post-Approval Study questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and benefit before the device can be found approvable and any post-approval study could be considered.

The Applicant did not provide a PAS proposal for FDA review in the original submission for subject device. In addition, in their response to FDA major deficiency letter, the Applicant provided a justification for why they did not believe a post approval study is necessary. In the response, the Applicant states that: (1) adequate performance data was obtained during the premarket review process; (2) additional longer-term performance data is not required due to the long history of the Crystalens platform across a broad population of diverse populations; (3) over a decade of use in over 315,000 patients has established the safety profile of the Crystalens IOLs; and (4) the toric version of the Crystalens IOL in the requested ranges have not created any new safety or effectiveness concerns.

If the device were to be approved, FDA believes a post approval study is necessary because this is a permanent implant that is a first-of-a-kind device, due to its combined toric and accommodative features. Therefore, postmarket evaluation of device performance is needed in a larger population and in real-world setting. Through premarket review of the PMA, FDA has identified the following postmarket concerns and recommends that a PAS be conducted to assess the following:

- Evaluation of long term device safety in the real-world experience, specifically vault change, or z-syndrome; and evaluation of the impact of age on device performance.

The issues noted below are FDA's questions regarding potential post-approval studies for the Panel.

Since this is a first of a kind IOL, due to its combined toric and accommodative features, and the permanent implant nature, there are concerns about the frequency and severity of adverse events and possible increase in frequency and/or worsen severity over time. In addition, there are concerns regarding device performance in certain groups. Therefore, considering the long-term safety and the risk/benefit profile of the device, please address the following:

a. **Discuss if there is need for evaluation of device long term safety and what would be an appropriate length of follow-up.**

b. **Discuss if there is need for evaluation of device performance under real-world conditions with a new enrollment cohort of patients treated in the commercial setting.**

c. **Discuss if there are other adverse events besides those listed in the IDE study that are important and should be assessed in the postmarket setting.**

d. **The premarket data shows a statistically significant difference on the treatment effect (difference between the test and control arms for "percent reduction in cylinder") by age. The treatment effect is negative among those younger than 60 and positive for those 60 years old and older. Please discuss if there is need to evaluate the impact of age on the device performance among subjects newly treated in the postmarket setting.**

Table 1: Model AT-45 Biocompatibility Testing [redacted])

Test Description	Results	Applicable Standard
Cytotoxicity: Agar Diffusion Cell Growth Inhibition	Non-cytotoxic	ISO 10993-5
Genotoxicity: Reverse Mutation Assay (Ames Test)	Non-mutagenic	ISO 10993-3
Maximization Sensitization Test (Kligman)	Non-sensitizing	ISO 10993-10
Acute Systemic Toxicity (Systemic Injection)	Passed	ISO 10993-11
Non-ocular Implantation Study (Rabbit Muscle)	Passed	ISO 10993-6
Ocular Implantation	Passed	ISO 10993-6
ND:YAG Laser Test	Passed	ISO/DIS 11979-5
Test of Extractables and Hydrolytic Stability	Passed	ISO/DIS 11979-5
Test of Extractables by Exhaustive Extraction	Passed	ISO/DIS 11979-6
Photostability Test	Passed	ISO/DIS 11979-5

Table 2: Biocompatibility Testing [redacted])

Test Description	Results	Applicable Standards
Cytotoxicity: MEM Elution	Non-cytotoxic	ISO 10993-5
Genotoxicity: Reverse Mutation Assay (Ames Test)	Non-mutagenic	ISO 10993-3
Maximization Sensitization Test (Kligman)	Non-sensitizing	ISO 10993-10
Acute Systemic Toxicity (Systemic Injection)	Passed	ISO 10993-11
Non-ocular Implantation Study (Rabbit Muscle)	Passed	ISO 10993-6
Ocular Implantation	Passed	ISO 10993-6
Irritation – Intracutaneous Reactivity	Passed	ISO 10993-10
ND:YAG Laser Test	Passed	ISO/DIS 11979-5
Test of Extractables and Hydrolytic Stability	Passed	ISO/DIS 11979-5
Test of Extractables by Exhaustive Extraction	Passed	ISO/DIS 11979-6
Photostability Test	Passed	ISO/DIS 11979-5

Table 3: Adverse Events in Parent IOL Study*

Adverse Event	Cumulative	FDA Grid	Persistent	FDA Grid
Endophthalmitis	1/324 (0.3%)	0.1%	----	----
Hyphema	11324 (0.3%)	2.2%	----	----
Hypopyon	0/324	0.3%	----	----
IOL Dislocation	0/324	0.1%	----	----
Cystoid Macular Edema	12/324 (3.7%)	3.0%	2/304 (0.7%)	0.5%
Pupillary Block	0/324	0.1%	----	----
Retinal Detachment	0/324	0.3%	----	----
Secondary Surgical Reintervention	2/324 (0.6%)	0.8%	----	----
Corneal Edema	----		0/298	0.3%
Iritis	----		2/298 (0.7%)	0.3%
Raised lOP Requiring Treatment	----		0/304	0.4'%

*From Summary of Safety and Effectiveness (SSED) for Parent IOL

Table 4: Schedule of visits and procedures

	Pre-Op Day-90-0	**Operative Day 0**	**Form 1 1-2 Days**	**Form 2 7-14 Days**	**Form 3 30-60 Days**	**Form 4 120-180 Days**	**Form 5 245-301 Days**	**Form 6 330-420 Days**
Informed Consent	X							
Demographics	X							
Eligibility	X	X						
Randomization		X						
Surgery		X						
Dilated Pupil Size	X							
Potential Acuity	X							
Uncorrected Distance VA	X		X	X	X	X	X	X
Uncorrected Intermediate VA (80cm/32in)	X			X	X	X	X	X
Uncorrected Near VA (40cm/16in)	X		X	X	X	X	X	X
Manifest Refraction	X			X	X	X	X	X
BCVA without glare	X				X	X	X	X

Table 5: Accountability of Subjects at Each Form Visit (All Enrolled)

Subject Status	Preop Exam n (%)	Op Report n (%)	Form 1 n (%)	Form 2 n (%)	Form 3 n (%)	Form 4 n (%)
Available for Analysis	229 (100.0)	229 (100.0)	227 (99.1)	223 (97.4)	219 (95.6)	211 (92.1)
Discontinued	0	0	2 (0.9)	3 (1.3)	3 (1.3)	3 (1.3)
Missing at scheduled visit but seen later	0	0	0	3 (1.3)	7 (3.1)	0
Not seen but accounted for	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Active	0	0	0	0	0	15 (6.6)
Percent Accountability			(100.0)	(98.7)	(96.9)	(100.0)

Notes: Percentages are based on the number of enrolled subjects.
Percent accountability = 100 x Available for Analysis / (Enrolled – Discontinued – Active)

Table 6: Accountability of Subjects at Each Form Visit by IOL (All Enrolled)

	Control IOL (Enrolled, N=76)						Toric IOL 1.25 D (Enrolled, N=82)						Toric IOL 2.00 D (Enrolled, N=47)						Toric IOL 2.75 D (Enrolled, N=24)					
Subject Status	**Preop n (%)**	**Op n (%)**	**Form 1 n (%)**	**Form 2 n (%)**	**Form 3 n (%)**	**Form 4 n (%)**	**Preop n (%)**	**Op n (%)**	**Form 1 n (%)**	**Form 2 n (%)**	**Form 3 n (%)**	**Form 4 n (%)**	**Preop n (%)**	**Op n (%)**	**Form 1 n (%)**	**Form 2 n (%)**	**Form 3 n (%)**	**Form 4 n (%)**	**Preop n (%)**	**Op n (%)**	**Form 1 n (%)**	**Form 2 n (%)**	**Form 3 n (%)**	**Form 4 n (%)**
Available for Analysis	76 (100.0)	76 (100.0)	76 (100.0)	75 (98.7)	74 (97.4)	69 (90.8)	82 (100.0)	82 (100.0)	80 (97.6)	79 (96.3)	78 (95.1)	74 (90.2)	47 (100.0)	47 (100.0)	47 (100.0)	45 (95.7)	45 (95.7)	46 (97.9)	24 (100.0)	24 (100.0)	24 (100.0)	24 (100.0)	22 (91.7)	22 (91.7)
Discontinued	0	0	0	1 (1.3)	1 (1.3)	1 (1.3)	0	0	2 (2.4)	2 (2.4)	2 (2.4)	2 (2.4)	0	0	0	0	0	0	0	0	0	0	0	0
Missing at scheduled visit but seen later	0	0	0	0	1 (1.3)	0	0	0	0	1 (1.2)	2 (2.4)	0	0	0	0	2 (4.3)	2 (4.3)	0	0	0	0	0	2 (8.3)	0
Not seen but accounted for	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Active	0	0	0	0	0	6 (7.9)	0	0	0	0	0	6 (7.3)	0	0	0	0	0	1 (2.1)	0	0	0	0	0	2 (8.3)
Percent Accountability			(100.0)	(100.0)	(98.7)	(100.0)			(100.0)	(98.8)	(97.5)	(100.0)			(100.0)	(95.7)	(95.7)	(100.0)			(100.0)	(100.0)	(91.7)	(100.0)

Notes: Percentages are based on the number of enrolled subjects.
Percent accountability = 100 x Available for Analysis / (Enrolled - Discontinued - Active

Table 7: Number of Implanted Effectiveness Eyes Available at Form 4 by Cylinder Power

	All Effectiveness Eyes	AT-52 Eyes Excluded
Cylinder Power		
0.00 D (Sphere Control)	68	64
1.25 D	74	69
2.00 D	40	40
2.75 D	21	20

Table 8: Demographics

	Control IOL (N=76)	Toric IOL 1.25 D (N=82)	Toric IOL 2.00 D (N=47)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=153)
Age (years)					
Total Non-Missing	76	82	47	24	153
Mean (SD)	69.8 (9.2)	69.9 (8.8)	70.4 (8.4)	70.4 (10.8)	70.1 (9.0)
Median	71.0	70.0	70.0	73.0	70.0
Min, Max	47, 89	48, 88	52, 89	51, 8	48, 89
< 60	13 (17.1%)	8 (9.8%)	3 (6.4%)	5 (20.8%)	16 (10.5%)
60 to 69	20 (26.3%)	32 (39.0%)	2 (42.6%)	5 (20.8%)	57 (37.3%)
70 to 79	34 (44.7%)	27 (32.9%)	15 (31.9%)	7 (29.2%)	49 (32.0%)
80	9 (11.8%)	15 (18.3%)	9 (19.1%)	7 (29.2%)	31 (20.3%)
Missing	0	0	0	0	0
Gender					
Total Non-Missing	76	82	47	24	153
Male	34 (44.7%	35 (42.7%)	27 (57.4%)	10 (41.7%)	72 (47.1%)
Female	42 (55.3)	47 (57.3%)	20 (42.6%)	14 (58.3%)	81 (52.9%)
Missing	0	0	0	0	0
Operative Eye					
Total Non-Missing	76	82	47	24	153
OD	42 (55.3)	37 (45.1%)	25 (53.2%)	12 (50.0%)	74 (48.4%)
OS	34 (44.7%)	45 (54.9%)	22 (46.8%)	12 (50.0%)	79 (51.6%)
Missing	0	0	0	0	0

Table 9: Preoperative and Predicted Corneal Cylinder (Effectiveness Cohort)

	Sphere IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Preoperative Corneal Cylinder (D)					
Total Non-Missing	73	77	41	24	142
Mean (SD)	1.504 (0.137)	1.532 (0.144)	2.033 (0.126)	2.590 (0.199)	1.856 (0.424)
Median	1.460	1.500	2.020	2.530	1.785
Min, Max	1.34, 1.80	1.33, 1.81	1.83, 2.30	2.34, 3.00	1.33, 3.00
Missing	0	0	0	0	0
Predicted Postop Corneal Cylinder (D)					
Total Non-Missing	73	77	41	24	142
Mean (SD)	1.004 (0.137)	1.032 (0.144)	1.533 (0.126)	2.090 (0.199)	1.356 (0.424)
Median	0.960	1.000	1.520	2.030	1.285
Min, Max	0.84, 1.30	0.83, 1.31	1.33, 1.80	1.84, 2.50	0.83, 2.50
Missing	0	0	0	0	0

Table 10: Preoperative and Predicted Refractive Cylinder (Effectiveness Cohort)

	Sphere IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Preoperative Refractive Cylinder (D)					
Total Non-Missing	73	77	41	24	142
Mean (SD)	-1.288 (0.719)	-1.315 (0.747)	-1.756 (0.643)	-2.073 (0.697)	-1.570 (0.766)
Median	-1.250	-1.250	-1.750	-2.250	-1.500
Min, Max	-3.25, 0.00	-3.00, 0.00	-3.00, 0.00	-4.00, -1.00	-4.00, 0.00
Missing	0	0	0	0	0
Predicted Postop Refractive Cylinder (D)**					
Total Non-Missing	73	77	41	24	142
Mean (SD)	0.183 (0.157)	0.211 (0.180)	0.197 (0.128)	0.258 (0.196)	0.215 (0.170)
Median	0.130	0.170	0.190	0.200	0.180
Min, Max	0.01, 0.85	0.00, 1.15*	0.00, 0.47	0.01, 0.64	0.00, 1.15
Missing	0	0	0	0	0

* This subject's (650110193003) expected post-op corneal cylinder was entered in the expected post-op manifest cylinder field on the CRF. It was later corrected to 0.32 D.

**Predicted postoperative refractive cylinder is absolute cylinder at the corneal plane.

Table 11: Potential Range of Cylinder in Each Study Arm

IOL Cyl Power	Power at the Corneal Plane	Range of Predicted Postoperative Corneal Cylinder	Preoperative Corneal Cylinder
1.25D	0.83D	0.83 – 1.32D	1.33 – 1.82 D
2.00D	1.33D	1.33 – 1.82D	1.83 – 2.32 D
2.75D	1.83D	1.83D – 2.50*	3.00*

**based upon inclusion criterion #6 and the expectation of 0.50 D incisional effect*

Table 12: Protocol Deviations

Type of Deviation	# of deviations
Major	**24**
Failed to meet inclusion criteria	11
Noncompliance with surgical procedure	3
Implant of AT52T/SE IOLs	10
Minor	**377**
Protocol assessments not performed	151
Protocol procedures/assessments done incorrectly/incompletely	105
Documentation practices	82
Out-of-window visit	22
Informed consent issues	15
Missed visit	2
Overall Total	**401**

Table 13: BCDVA at Each Examination (All Toric IOLs, Implanted Safety Cohort Subjects)

	Preop	Form 3	Form 4	Unscheduled
20/40 or Better	108 (72.0%)	143 (99.3%)	139 (97.9%)	32 (97.0%)
Worse than 20/40	42 (28.0%)	1 (0.7%)	3 (2.1%)	1 (3.0%)

Table 14: Subjects Experiencing a BCVA Decrease of 10 Letters or More Between an Evaluation and a Later Evaluation, Implanted Subjects (Safety Cohort)

	Control IOL (N=76) n (%)	Toric IOL 1.25 D (N=80) n (%)	Toric IOL 2.00 D (N=47) n (%)	Toric IOL 2.75 D (N=24) n (%)	All Toric IOL (N=151) n (%)
Total Number of Subjects Experiencing Decrease in VA = 10 Letters During the Study	**1 (1.3)**	**1 (1.3)**	**4 (8.5)**	**1 (4.2)**	**6 (4.0)**
Number of Subjects with Decrease in VA 10 Letters From a Previous Visit by Form					
Form 3	0	0	0	0	0
Form 4	1 (1.3)	1 (1.3)	2 (4.3)	1 (4.2)	4 (2.6)
Unscheduled	0	0	2 (4.3)	0	2 (1.3)

Table 15: BCNVA at Each Examination (All Toric IOLs, Implanted Safety Cohort Subjects)

	Preop	Form 3	Form 4	Unscheduled
20/40 or Better	124 (89.2%)	141 (98.6%)	142 (100.0%)	24 (100.0%)
Worse than 20/40	15 (10.8%)	2 (1.4%)	0	0

Table 16: ISO SPE Adverse Events Reported at Each Postoperative Visit (Implanted Sphere Subjects)

Adverse Event	Unscheduled n/N (%)	Form 1 n/N (%)	Form 2 n/N (%)	Form 3 n/N (%)	Form 4 n/N (%)	Form 5 n/N (%)	Form 6 n/N (%)	Cumulative n/N (%)	p-value
Cumulative									
Endophthalmitis	0/44	0/76	0/75	0/74	0/72	0/70	0/69	0/76	>0.999
Hypopyon	0/44	0/76	0/75	0/74	0/72	0/70	0/69	0/76	>0.999
Lens Dislocated From Posterior Chamber	0/44	0/76	0/75	0/74	0/72	0/70	0/69	0/76	>0.999
Macular Edema	0/44	0/76	0/75	1/74 (1.4)	1/73 (1.4)	0/70	0/69	1/76 (1.3)	0.901
Pupillary Block	0/44	0/76	0/75	0/74	0/72	0/70	0/69	0/76	>0.999
Retinal Detachment	0/44	0/76	0/75	0/74	0/72	0/70	0/69	0/76	>0.999
Secondary Surgical Intervention	1/44 (2.3)	0/76	1/75 (1.3)	0/74	0/72	1/70 (1.4)	0/69	3/76 (3.9)	0.023
Persistent									
Corneal Edema							0/69		>0.999
Iritis							0/69		>0.999
Macular Edema							0/69		>0.999
Raised IOP Requiring Treatment							0/69		>0.999

Notes: The p-value is calculated from the exact binomial test comparing the cumulative or persistent (at Form 6) proportion of eyes with each adverse event to the ISO SPE proportion (1-sided test). The ISO SPE proportions for cumulative AEs are: endophthalmitis (0.1%), hypopyon (0.3%), lens dislocated from posterior chamber (0.1%), macular oedema (3.0%), pupillary block (0.1%), retinal detachment (0.3%), and secondary surgical intervention (0.8%); and for persistent are: macular oedema (0.5%), corneal oedema (0.3%), iritis (0.3%), and raised IOP requiring treatment (0.4%).

Table 17: ISO SPE Adverse Events Reported at Each Postoperative Visit (All Implanted Toric Subjects)

Adverse Event	Unscheduled n/N (%)	Form 1 n/N (%)	Form 2 n/N (%)	Form 3 n/N (%)	Form 4 n/N (%)	Form 5 n/N (%)	Form 6 n/N (%)	Cumulative n/N (%)	p-value
Cumulative									
Endophthalmitis	0/77	0/151	0/148	0/145	0/147	0/145	0/143	0/151	>0.999
Hypopyon	0/77	0/151	0/148	0/145	0/147	0/145	0/143	0/151	>0.999
Lens Dislocated From Posterior Chamber	0/77	0/151	0/148	0/145	0/147	0/145	0/143	0/151	>0.999
Macular Edema	0/77	0/151	0/148	1/145 (0.7)	1/147 (0.7)	0/145	0/143	1/151 (0.7)	0.990
Pupillary Block	0/77	0/151	0/148	0/145	0/147	0/145	0/143	0/151	>0.999
Retinal Detachment	0/77	0/151	0/148	0/145	0/147	0/145	0/143	0/151	>0.999
Secondary Surgical Intervention	1/77 (1.3)	0/151	0/148	0/145	1/147 (0.7)	0/145	0/143	2/151 (1.3)	0.341
Persistent									
Corneal Edema							0/143		>0.999
Iritis							0/143		>0.999
Macular Edema							0/143		>0.999
Raised IOP Requiring Treatment							0/143		>0.999

Notes: The p-value is calculated from the exact binomial test comparing the cumulative or persistent (at Form 6) proportion of eyes with each adverse event to the ISO SPE proportion (1-sided test). The ISO SPE proportions for cumulative AEs are: endophthalmitis (0.1%), hypopyon (0.3%), lens dislocated from posterior chamber (0.1%), macular oedema (3.0%), pupillary block (0.1%), retinal detachment (0.3%), and secondary surgical intervention (0.8%); and for persistent are: macular oedema (0.5%), corneal oedema (0.3%), iritis (0.3%), and raised IOP requiring treatment (0.4%).

Table 18: Surgical Adverse Events, Implanted Subjects (Safety Cohort)

	Control IOL (N-76) n (%)	Toric IOL 1.25 D (N=80) n (%)	Toric IOL 2.00 D (N=47) n (%)	Toric IOL 2.75 D (N=24) n (%)	All Toric IOL (N=151) n (%)
Total Number of AEs	3	2	3	0	5
Number of Subjects with ≥1 AE	2 (2.6)	2 (2.5)	3 (6.4)	0	3 (2.0)
Eye disorders	1 (1.3)	1 (1.3)	2 (4.3)	0	0
Corneal disorder	1 (1.3)	0	0	0	0
Foreign body sensation in eyes	0	0	1 (2.1)	0	1 (0.7)
Hordeolum	0	0	1 (2.1)	0	1 (0.7)
Iris atrophy	0	1 (1.3)	0	0	1 (0.7)
Injury, poisoning and procedural complications	2 (2.6)	1 (1.3)	1 (2.1)	0	2 (1.3)
Cataract operation complication	2 (2.6)	0	0	0	0
Incision site complication	0	0	1 (2.1)	0	1 (0.7)
Posterior capsule rupture	0	1 (1.3)	0	0	1 (0.7)

Notes: The total number of adverse events counts all adverse events for subjects. Subjects may have more than one adverse event per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported one or more events.

Table 19: Primary, Secondary, and Other Key Effectiveness Results*

	All Effectiveness Eyes			AT-50 Effectiveness Eyes Only		
	Sphere	1.25 D	All Toric	Sphere	1.25 D	All Toric
Primary Effectiveness Endpoints						
Percent Reduction in Cylinder, mean	46.5	79.9	85.0	45.4	81.2	85.6
Percent Reduction in Cylinder, p-value		<0.001			<0.001	
% of Eyes with Reduction in Cylinder within 0.50 D of intended	44.1	79.7	80.0	45.3	79.7	79.1
% of Eyes with Reduction in Cylinder within 1.00 D of intended	72.1	95.9	92.5	70.3	95.7	95.3
Absolute Value of Lens Axis Misalignment, mean	3.3	2.5	3.0	3.3	2.5	3.0
Secondary Effectiveness Endpoints						
logMAR DCIVA, mean	0.074	0.060	0.055	0.074	0.060	0.056
logMAR DCNVA, mean	0.309	0.308	0.301	0.307	0.309	0.304
logMAR CNVA, mean	0.045	0.039	0.037	0.046	0.043	0.039
BCVA, % of Eyes 20/40 or Better	100.0	100.0	99.3	100.0	100.0	99.2
logMAR UDVA, mean	0.189	0.099	0.096	0.190	0.090	0.092
logMAR UIVA, mean	0.069	0.044	0.042	0.075	0.046	0.045
logMAR UNVA, mean	0.286	0.284	0.288	0.288	0.294	0.296
Other Key Analyses						
% of eyes rotating less than or equal to 5°	--	100.0	100.0	--	100.0	100.0
Manifest refraction cylinder (D), mean	-0.89	-0.48	-0.44	-0.90	-0.46	-0.43

*Please note that the "all effectiveness eyes" columns include subjects implanted with AT-52 SE and AT-52 lenses which were not approved for use in this protocol.

Table 20: Toric IOL Cylinder Powers and Selection Criteria

IOL Cyl Power	Power at the Corneal Plane	Range of Preoperative Corneal Cylinder for toric model implantation	Range of Predicted Postoperative Corneal Cylinder [3rd col - 0.50D)]	Intended Postoperative Manifest Refractive Cylinder [4th col – 2nd col]
1.25D	0.83D	1.33 – 1.82 D	0.83 – 1.32D	0 – 0.49 D
2.00D	1.33D	1.83 – 2.32 D	1.33 – 1.82D	0 – 0.49 D
2.75D	1.83D	3.00*	1.83D – 2.50*	0 – 0.67 D

**based upon inclusion criterion #6 and the expectation of 0.50 D incisional effect*

Table 21: Percent Reduction in Absolute Cylinder at Form 4 by Age

	Toric IOL 1.25 D		Sphere IOL		Treatment Effect
	n	Mean	n	Mean	Mean
Age Group					
<60	7	54.846	11	67.780	-12.935
60 to 69	27	87.045	17	64.602	22.443
70 to 79	23	76.694	31	32.211	44.483
80 or older	14	89.759	7	30.638	59.121
Model P-Values					
Treatment	< 0.001				
Age Group	0.046				
Treatment x Age Group	0.012				

Table 22: Percent Reduction in Absolute Cylinder at Form 4 by Gender

	Toric IOL 1.25 D		Sphere IOL		Treatment Effect
	n	Mean	n	Mean	Mean
Gender					
Male	28	83.289	30	36.584	46.705
Female	43	79.596	36	54.425	25.171
Model P-Values					
Treatment	< 0.001				
Gender	0.285				
Treatment x Gender	0.104				

Table 23: Percent of Eyes with Reduction in Cylinder within 0.50 D and 1.00 D of Intended at Form 4

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Total Non-Missing	66	71	40	22	133
Within 0.50 D of Intended	**30 (45.5%)**	**58 (81.7%)**	**32 (80.0%)**	**16 (72.7%)**	**106 (79.7%)**
95% CI	(33.1%, 58.2%)	(70.7%, 89.9%)	(64.4%, 90.9%)	(49.8%, 89.3%)	(71.9%, 86.2%)
Within 1.00 D of Intended	**48 (72.7%)**	**68 (95.8%)**	**37 (92.5%)**	**22 (100.0%)**	**127 (95.5%)**
95% CI	(60.4%, 83.0%)	(88.1%, 99.1%)	(79.6%, 98.4%)	(84.6%, 100.0%)	(90.4%, 98.3%)
Notes: 95% CIs are exact binomial CIs.					

Table 24: Absolute Value of Lens Axis Misalignment from Surgical Markings – Form 4 (Effectiveness Cohort)

	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Total Non-Missing	69	37	20	126
Mean (SD)	2.594 (2.578)	2.144 (1.988)	3.243 (2.729)	2.565 (2.452)
Median	1.72	1.470	2.230	1.828
Min, Max	0.06, 12.52	0.14, 6.78	0.64, 10.48	0.06, 12.52
Missing	2	3	2	7
Less than 5°	59 (85.5%)	32 (86.5%)	16 (80.0%)	107 (84.9%)
Less than 10°	67 (97.1%)	37 (100.0%)	19 (95.0%)	123 (97.6%)
Less than 20°	69 (100.0%)	37 (100.0%)	20 (100.0%)	126 (100.0%)
Less than or equal to 30°	69 (100.0%)	37 (100.0%)	20 (100.0%)	126 (100.0%)
Greater than 30°	0	0	0	0

Table 25: Signed Value of Lens Axis Misalignment from Surgical Markings – Form 4 (Effectiveness Cohort, All Eyes)

	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Total Non-Missing	69	37	20	126
Mean (SD)	-0.289 (3.659)	-0.310 (2.929)	-0.187 (4.299)	-0.279 (3.545)
Median	-0.550	0.140	-1.590	-0.352
Min, Max	-10.27, 12.52	-6.76, 6.78	-8.85, 10.48	-10.27, 12.52
-15.00 to -10.01	1 (1.4%)	0	0	1 (0.8%)
-10.00 to - 5.01	5 (7.2%)	4 (10.8%)	1 (5.0%)	10 (7.9%)
- 5.00 to - 0.01	32 (46.4%)	14 (37.8%)	11 (55.0%)	57 (45.2%)
0	0	0	0	0
0.01 to 5.00	27 (39.1%)	18 (48.6%)	5 (25.0%)	50 (39.7%)
5.01 to 10.00	3 (4.3%)	1 (2.7%)	2 (10.0%)	6 (4.8%)
10.01 to 15.00	1 (1.4%)	0	1 (5.0%)	2 (1.6%)
Missing	2	3	2	7
Tolerance Interval	(-7.4, 6.8)	(-6.4, 5.8)	(-10.1, 9.7)	(-6.8, 6.3)

Notes: The tolerance interval is a two-sided tolerance interval around the mean of the signed value which contains at least 90% of the population with 95% probability.

Table 26: Absolute Value of Lens Axis Misalignment from Target By Direct Measurement – Form 4 (Effectiveness Cohort)

	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Total Non-Missing	70	38	21	129
Mean (SD)	5.057 (3.862)	3.792 (2.362)	5.514 (4.650)	4.759 (3.668)
Median	4.184	4.004	4.023	4.043
Min, Max	0.17, 16.86	0.12, 8.41	0.02, 17.12	0.02, 17.12
Missing	1	2	1	4
Less than 5°	38 (54.3%)	26 (68.4%)	12 (57.1%)	76 (58.9%)
Less than 10°	62 (88.6%)	38 (100.0%)	18 (85.7%)	118 (91.5%)
Less than 20°	70 (100.0%)	38 (100.0%)	21 (100.0%)	129 (100.0%)
Less than or equal to 30°	70 (100.0%)	38 (100.0%)	21 (100.0%)	129 (100.0%)
Greater than 30°	0	0	0	0

Table 27: Signed Value of Lens Axis Misalignment from Target by Direct Measurement - Form 4 (Effectiveness Cohort, All Eyes)

	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Total Non-Missing	70	38	21	129
Mean (SD)	0.297 (6.385)	-1.123 (4.365)	-2.135 (6.983)	-0.517 (6.000)
Median	0.469	-1.490	-0.017	-0.525
Min, Max	-16.86, 16.56	-8.41, 7.08	-17.12, 11.84	-17.12, 16.56
-20.00 to -15.01	1 (1.4%)	0	1 (4.8%)	2 (1.6%)
-15.00 to -10.01	3 (4.3%)	0	1 (4.8%)	4 (3.1%)
-10.00 to - 5.01	9 (12.9%)	8 (21.1%)	5 (23.8%)	22 (17.1%)
- 5.00 to - 0.01	19 (27.1%)	18 (47.4%)	4 (19.0%)	41 (31.8%)
0	0	0	0	0
0.01 to 5.00	20 (28.6%)	8 (21.1%)	8 (38.1%)	36 (27.9%)
5.01 to 10.00	14 (20.0%)	4 (10.5%)	1 (4.8%)	19 (14.7%)
10.01 to 15.00	3 (4.3%)	0	1 (4.8%)	4 (3.1%)
15.01 to 20.00	1 (1.4%)	0	0	1 (0.8%)
Missing	1	2	1	4
Tolerance Interval	(-12.0, 12.6)	(-10.1, 7.9)	(-18.1, 13.8)	(-11.6, 10.5)

Notes: The tolerance interval is a two-sided tolerance interval around the mean of the signed value which contains at least 90% of the population with 95% probability.

Table 28: UCDVA – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
UCDVA (logMAR)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	0.185 (0.181)	0.096 (0.128)	0.092 (0.135)	0.100 (0.134)	0.095 (0.130)
Median	0.204	0.097	0.097	0.097	0.097
Min, Max	-0.10, 0.50	-0.10, 0.40	-0.20, 0.50	-0.10, 0.30	-0.20, 0.50
Missing	0	0	0	0	0

Table 29: UCIVA – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
UCDVA (logMAR)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	0.085 (0.143)	0.046 (0.113)	0.074 (0.141)	0.049 (0.079)	0.055 (0.118)
Median	0.000	0.000	0.097	0.000	0.000
Min, Max	-0.10, 0.50	-0.30, 0.40	-0.30, 0.50	-0.10, 0.30	-0.30, 0.50
Missing	0	0	0	0	0

Table 30: UCNVA – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
UCDVA (logMAR)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	0.285 (0.138)	0.288 (0.148)	0.305 (0.144)	0.269 (0.146)	0.290 (0.146)
Median	0.301	0.301	0.301	0.301	0.301
Min, Max	0.00, 0.70	0.00, 0.70	0.00, 0.70	0.00, 0.60	0.00, 0.70
Missing	0	0	0	0	0

Table 31: Mean Uncorrected Acuity Results for Randomized Eyes

	Toric IOL (1.25 D)	Spherical IOL (control)
Distance Uncorrected VA	0.096	0.185
Intermediate Uncorrected VA (80 cm)	0.046	0.085
Near Uncorrected VA (40 cm)	0.288	0.285

Table 32: UCDVA Comparison at Form 4 with Adjustment for MRSE

(from Attachment C, Table 6.1)

	Toric IOL 1.25 D	Sphere IOL	Toric minus Sphere	P-value
logMAR UCDVA				
LS Mean (SE)	0.109 (0.016)	0.178 (0.017)	-0.069 (0.024)	0.004
95% C.I.	(0.077, 0.141)	(0.145, 0.212)	(-0.116, -0.022)	
p-values of Covariates				
MRSE	0.608			
MRSE*MRSE	< 0.001			

Table 33: UCIVA comparison at Form 4 with Adjustment for MRSE

(from Attachment C, Table 7.1)

	Toric IOL 1.25 D	Sphere IOL	Toric minus Sphere	P-value
logMAR UCIVA				
LS Mean (SE)	0.056 (0.034)	0.093 (0.034)	-0.037 (0.019)	0.053
95% C.I.	(0.012, 0.123)	(0.025, 0.161)	(0.075, 0.000)	
p-values of Covariates				
MRSE	< 0.001			
MRSE*MRSE	0.024			

Table 34: UCNVA Comparison at Form 4 with Adjustment for MRSE

	Toric IOL 1.25 D	Sphere IOL	Toric minus Sphere	P-value
logMAR UCNVA				
LS Mean (SE)	0.299 (0.026)	0.317 (0.026)	-0.018 (0.021)	0.403
95% C.I.	(0.249, 0.350)	(0.266, 0.368)	(0.061, 0.024)	
p-values of Covariates				
MRSE	< 0.001			
MRSE*MRSE	0.177			

Table 35: DCIVA at 32 inches (80 cm) – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
DCIVA (logMAR)					
Total Non-Missing	65	71	39	22	132
Mean (SD)	0.090 (0.125)	0.063 (0.103)	0.084 (0.125)	0.077 (0.11)	0.071 (0.111)
Median	0.097	0.097	0.097	0.097	0.097
Min, Max	-0.10, 0.50	-0.10, 0.30	-0.30, 0.30	-0.10, 0.30	-0.30, 0.30
Missing	1	0	1	0	1
DCIVA (Snellen)					
Total Non-Missing	65	71	39	22	132
20/20 or Better	27 (41.5%)	32 (45.1%)	10 (25.6%)	10 (45.5%)	52 (39.4%)
20/21 to 20/25	23 (35.4%)	29 (40.8%)	21 (53.8%)	7 (31.8%)	57 (43.2%)
20/26 to 20/32	8 (12.3%)	5 (7.0%)	5 (12.8%)	3 (13.6%)	13 (9.8%)
20/33 to 20/40	4 (6.2%)	5 (7.0%)	3 (7.7%)	2 (9.1%)	10 (7.6%)
20/40 or Better	62 (95.4%)	71 (100.0%)	39 (100.0%)	22 (100.0%)	132 (100.0%)
20/41 to 20/80	3 (4.6%)	0	0	0	0
20/81 to 20/100	0	0	0	0	0
20/101 to 20/200	0	0	0	0	0
Worse than 20/200	0	0	0	0	0
Missing	1	0	1	0	1
P-value*					
Control vs. All Toric	0.665				

* unplanned analysis

Table 36: DCNVA at 16 inches (40 cm) with Add – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
DCNVA with Add (logMAR)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	0.046 (0.073)	0.042 (0.075)	0.032 (0.066)	0.036 (0.073)	0.038 (0.071)
Median	0.000	0.000	0.000	0.000	0.000
Min, Max	-0.10, 0.30	-0.10, 0.30	-0.10, 0 20	-0.10, 0.20	-0.10, 0.30
Missing	0	0	0	0	0
DCIVA (logMAR)					
Total Non-Missing	66	71	40	22	133
20/20 or Better	41 (62.1%)	48 (67.6%)	29 (72.5%)	15 (68.2%)	92 (69.2%)
20/21 to 20/25	19 (28.8%)	17 (23.9%)	8 (20.0%)	5 (22.7%)	30 (22.6%)
20/26 to 20/32	5 (7.6%)	4 (5.6%)	3 (7.5%)	2 (9.1%)	9 (6.8%)
20/33 to 20/40	1 (1.5%)	2 (2.8%)	0	0	2 (1.5%)
20/40 or Better	66 (100.0%)	71 (100.0%)	40 (100.0%)	22 (100.0%)	133 (100.0%)
20/41 to 20/80	0	0	0	0	0
20/81 to 20/100	0	0	0	0	0
20/101 to 20/200	0	0	0	0	0
Worse than 20/200	0	0	0	0	0
Missing	0	0	0	0	0
P-value					
Control vs. All Toric	0.338				
Add (D)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	1.595 (0.580)	1.454 (0.446)	1.388 (0.537)	1.455 (0.630)	1.434 (0.505)
Median	1.500	1.500	1.500	1.500	1.500
Min, Max	0.00, 2.50	0.50, 2.50	0.00, 2.50	0.00, 2.50	0.00, 2.50
Missing	0	0	0	0	0
P-value*					
Control vs. All Toric	0.046				

* unplanned analysis

Table 37: BCDVA without Glare – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
BCDVA (logMAR)					
Total Non-Missing	66	71	40	22	133
Mean (SD)	0.011 (0.097)	0.006 (0.072)	0.002 (0.082)	0.018 (0.146)	0.007 (0.090)
Median	0.000	0.000	0.000	0.000	0.000
Min, Max	-0.10, 0.30	-0.20, 0.20	-0.20, 0.20	-0.20, 0.5	-0.20, 0.50
Missing	0	0	0	0	0
BCDVA (Snellen)					
Total Non-Missing	66	71	40	22	133
20/20 or Better	47 (71.2%)	55 (77.5%)	29 (72.5%)	14 (63.6%)	98 (73.7%)
20/21 to 20/25	14 (21.2%)	14 (19.7%)	1 (25.0%)	6 (27.3%)	30 (22.6%)
20/26 to 20/32	3 (4.5%)	2 (2.8%)	1 (2.5%)	1 (4.5%)	4 (3.0%)
20/33 to 20/40	2 (3.0%)	0	0	0	0
20/40 or Better	66 (100.0%)	71 (100.0%)	40 (100.0%)	21 (95.5%)	132 (99.2%)
20/41 to 20/80	0	0	0	1 (4.5%)	1 (0.8%)
20/81 to 20/100	0	0	0	0	0
20/101 to 20/200	0	0	0	0	0
Worse than 20/200	0	0	0	0	0
Missing	0	0	0	0	0
P-value*					
Control vs. All Toric	0.947				

*unplanned analysis

Table 38: BCDVA without Glare at Each Examination Compared to Historical Controls at 20/40 or Better (Effectiveness Cohort)

	Control IOL				Toric 1.25 IOL				Toric 2.00 IOL				Toric 2.75 IOL				All Toric IOL			
BCDVA	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL
Total Non-Missing	73	70	66		77	75	71		41	38	40		24	22	22		142	135	133	
20/20 or Better	9 (12.3)	51 (72.9)	47 (71.2)		9 (11.7)	57 (76.0)	55 (77.5)		2 (4.9)	30 (78.9)	29 (72.5)		1 (4.2)	16 (72.7)	14 (63.6)		12 (8.5)	103 (76.3)	98 (73.7)	
20/21 to 20/25	18 (24.7)	12 (17.1)	14 (21.2)		17 (22.1)	15 (20.0)	14 (19.7)		7 (17.1)	5 (13.2)	10 (25.0)		3 (12.5)	5 (22.7)	6 (27.3)		27 (19.0)	25 (18.5)	30 (22.6)	
20/26 to 20/32	15 (20.5)	4 (5.7)	3 (4.5)		20 (26.0)	1 (1.3)	2 (2.8)		16 (39.0)	3 (7.9)	1 (2.5)		3 (12.5)	1 (4.5)	1 (4.5)		39 (27.5)	5 (3.7)	4 (3.0)	
20/33 to 20/40	13 (17.8)	2 (2.9)	2 (3.0)		12 (15.6)	1 (1.3)	0		4 (9.8)	0	0		6 (25.0)	0	0		22 (15.5)	1 (0.7)	0	
20/40 or Better	55 (75.3)	69 (98.6)	66 (100.0)	>0.999 0.956 1.000	58 (75.3)	74 (98.7)	71 (100.0)	>0.999 0.959 1.000	29 (70.7)	38 (100.0)	40 (100.0)	>0.999 0.928 1.000	13 (54.2)	22 (100.0)	21 (95.5)	0.820 0.802 0.998	100 (70.4)	134 (99.3)	132 (99.2)	>0.999 0.965 1.000
20/41 to 20/80	17 (23.3)	1 (1.4)	0		18 (23.4)	0	0		10 (24.4)	0	0		11 (45.8)	0	1 (4.5)		39 (27.5)	0	1 (0.8)	
20/81 to 20/100	1 (1.4)	0	0		1 (1.3)	1 (1.3)	0		1 (2.4)	0	0		0	0	0		2 (1.4)	1 (0.7)	0	
20/101 to 20/200	0	0	0		0	0	0		1 (2.4)	0	0		0	0	0		1 (0.7)	0	0	
Worse than 20/200	0	0	0		0	0	0		0	0	0		0	0	0		0	0	0	
Missing	0	1	0		0	0	0		0	1	0		0	0	0		0	1	0	

Notes: The p-value is calculated from the exact binomial test comparing the proportion of eyes that presented a BCDVA of 20/40 or better at the Form 4 visit (1-sided test, alpha = 0.05) to the historical control rate (92.5%). The LCL and UCL represent the lower and upper limits, respectively, of a 90% confidence interval around the proportion of eyes with BCDVA 20/40 or better at Form 4.

Table 39: BCDVA without Glare at Each Examination Compared to Historical Controls at 20/40 or Better (Best Case Cohort)

	Control IOL				Toric I.25 IOL				Toric 2.00 IOL				Toric 2.75 IOL				All Toric IOL			
BCDVA	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL	Preop n (%)	Form 3 n (%)	Form 4 n (%)	p-value LCL UCL
Total Non-Missing	60	57	54		66	65	60		31	28	30		17	16	16		114	109	106	
20/20 or Better	7 (11.7)	42 (73.7)	39 (72.2)		9 (13.6)	51 (78.5)	48 (80.0)		1 (3.2)	22 (78.6)	20 (66.7)		1 (5.9)	12 (75.0)	9 (56.3)		11 (9.6)	85 (78.0)	77 (72.6)	
20/21 to 20/25	16 (26.7)	10 (17.5)	12 (22.2)		15 (22.7)	11 (16.9)	10 (16.7)		7 (22.6)	3 (10.7)	9 (30.0)		3 (17.6)	3 (18.8)	5 (31.3)		25 (21.9)	17 (15.6)	24 (22.6)	
20/26 to 20/32	14 (23.3)	4 (7.0)	3 (5.6)		17 (25.8)	1 (1.5)	2 (3.3)		12 (38.7)	3 (10.7)	1 (3.3)		3 (17.6)	1 (6.3)	1 (6.3)		32 (28.1)	5 (4.6)	4 (3.8)	
20/33 to 20/40	10 (16.7)	0	0		11 (16.7)	1 (1.5)	0		4 (12.9)	0	0		4 (23.5)	0	0		19 (16.7)	1 (0.9)	0	
20/40 or Better	47 (78.3)	56 (98.2)	54 (100.0)	>0.999 0.946 1.000	52 (78.8)	64 (98.5)	60 (100.0)	>0.999 0.951 1.000	24 (77.4)	28 (100.0)	30 (100.0)	>0.999 0.905 1.000	11 (64.7)	16 (100.0)	15 (93.8)	0.713 0.736 0.997	87 (76.3)	108 (99.1)	105 (99.1)	>0.999 0.956 1.000
20/41 to 20/80	12 (20.0)	1 (1.8)	0		14 (21.2)	0	0		6 (19.4)	0	0		6 (35.3)	0	1 (6.3)		26 (22.8)	0	1 (0.9)	
20/81 to 20/100	1 (1.7)	0	0		0	1 (1.5)	0		0	0	0		0	0	0		0	1 (0.9)	0	
20/101 to 20/200	0	0	0		0	0	0		1 (3.2)	0	0		0	0	0		1 (0.9)	0	0	
Worse than 20/200	0	0	0		0	0	0		0	0	0		0	0	0		0	0	0	
Missing	0	1	0		0	0	0		0	1	0		0	0	0		0	1	0	

Notes: The p-value is calculated from the exact binomial test comparing the proportion of eyes that presented a BCDVA of 20/40 or better at the Form 4 visit (1-sided test, alpha = 0.05) to the historical control rate (96.7%). The LCL and UCL represent the lower and upper limits, respectively, of a 90% confidence interval around the proportion of eyes with BCDVA 20/40 or better at Form 4.

Table 40: Rotational Stability between Consecutive Visits – Form 4 (All Eyes Attending the Two Consecutive Visits)

	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Absolute Value of Rotation (°)				
Total Non-Missing	66	35	20	121
Mean (SD)	1.135 (1.081)	1.153 (0.914)	1.640 (1.316)	1.224 (1.086)
Median	0.698	0.945	1.120	0.800
Min, Max	0.16, 5.18	0.04, 4.15	0.30, 4.38	0.04, 5.18
Missing	6	5	2	13
Lenses Rotating " ≤ 5° Since Last Visit	**65 (98.5%)**	**35 (100.0%)**	**20 (100.0%)**	**120 (99.2%)**

Table 41: Rotational Stability between Consecutive Visits – Form 4 (Consistent Cohort)

	Toric IOL 1.25 D (N=66)	Toric IOL 2.00 D (N=35)	Toric IOL 2.75 D (N=20)	All Toric IOL (N=121)
Absolute Value of Rotation (°)				
Total Non-Missing	66	35	20	121
Mean (SD)	1.135 (1.081)	1.153 (0.914)	1.640 (1.316)	1.224 (1.086)
Median	0.698	0.945	1.120	0.800
Min, Max	0.16, 5.18	0 04, 4.15	0.30, 4.38	0.04, 5.18
Missing	0	0	0	0
Lenses Rotating ≤ 5° Since Last Visit	**65 (98.5%)**	**35 (100.0%)**	**20 (100.0%)**	**120 (99.2%)**

Table 42: Surgically Induced Astigmatism – Form 4 (Effectiveness Cohort)

	Control IOL (N=73)	Toric IOL 1.25 D (N=77)	Toric IOL 2.00 D (N=41)	Toric IOL 2.75 D (N=24)	All Toric IOL (N=142)
Surgically Induced Astigmatism (D)					
Total Non-Missing	65	71	40	22	133
Mean (SD)	0.696 (0.467)	0.715 (0.480)	0.773 (0.501)	0.812 (0.526)	0.748 (0.492)
Median	0.608	0.670	0.728	0.790	0.688
Min, Max	0.10, 3.09	0.05, 2.80	0.07, 2.23	0.12, 2.05	0.05, 2.80
Missing	1	0	0	0	0
Change in Magnitude (D)					
Total Non-Missing	65	71	40	22	133
Mean (SD)	-0.337 (0.395)	-0.369 (0.414)	-0.429 (0.483)	-0.510 (0.596)	-0.410 (0.468)
Median	-0.360	-0.380	-0.415	-0.415	-0.400
Min, Max	-1.28, 0.72	-1.12, 0.74	-1.97, 0.39	-1.62, 0.95	-1.97, 0.95
Missing	1	0	0	0	0
Absolute Change in Axis (^{o})					
Total Non-Missing	65	71	40	22	133
Mean (SD)	11.4 (13.1)	11.0 (13.7)	9.0 (11.3)	5.2 (6.3)	9.5 (12.2)
Median	9.0	6.0	5.5	2.5	6.0
Min, Max	0, 64	0, 88	0, 59	0, 23	0, 88
0	3 (4.6%)	3 (4.2%)	1 (2.5%)	5 (22.7%)	9 (6.8%)
1 to 5	25 (38.5%)	27 (38.0%)	19 (47.5%)	10 (45.5%)	56 (42.1%)
6 to 10	11 (16.9%)	14 (19.7%)	7 (17.5%)	3 (13.6%)	24 (18.0%)
11 to 15	9 (13.8%)	13 (18.3%)	7 (17.5%)	2 (9.1%)	22 (16.5%)
16 to 20	9 (13.8%)	3 (4.2%)	3 (7.5%)	1 (4.5%)	7 (5.3%)
21 to 25	4 (6.2%)	6 (8.5%)	0	1 (4.5%)	7 (5.3%)
26 to 30	0	0	1 (2.5%)	0	1 (0.8%)
Greater than 30	4 (6.2%)	5 (7.0%)	2 (5.0%)	0	7 (5.3%)
Missing	1	0	0	0	0

Table 43: Error in the predicted magnitude of postoperative keratometric astigmatism at Form 4: bias and absolute error

	Randomized Eyes (N=150)
Signed Bias versus Predicted (D)	
Total Non-Missing	141
Mean (SD)	0.132 (0.398)
Median	0.120
Min, Max	-0.78, 1.24
Absolute Error (D)	
Total Non-Missing	141
Mean (SD)	0.335 (0.250)
Median	0.270
Min, Max	0.01, 1.24

Table 44: Error in the predicted postoperative keratometric steep axis at Form 4: bias and absolute error

	Randomized Eyes (N=150)
Signed Bias versus Predicted (degrees)	
Total Non-Missing	141
Mean (SD)	-0.1 (17.9)
Median	-1.0
Min, Max	-49, 88
Absolute Error (degrees)	
Total Non-Missing	141
Mean (SD)	11.7 (13.6)
Median	7.0
Min, Max	0, 88

Figure 1:

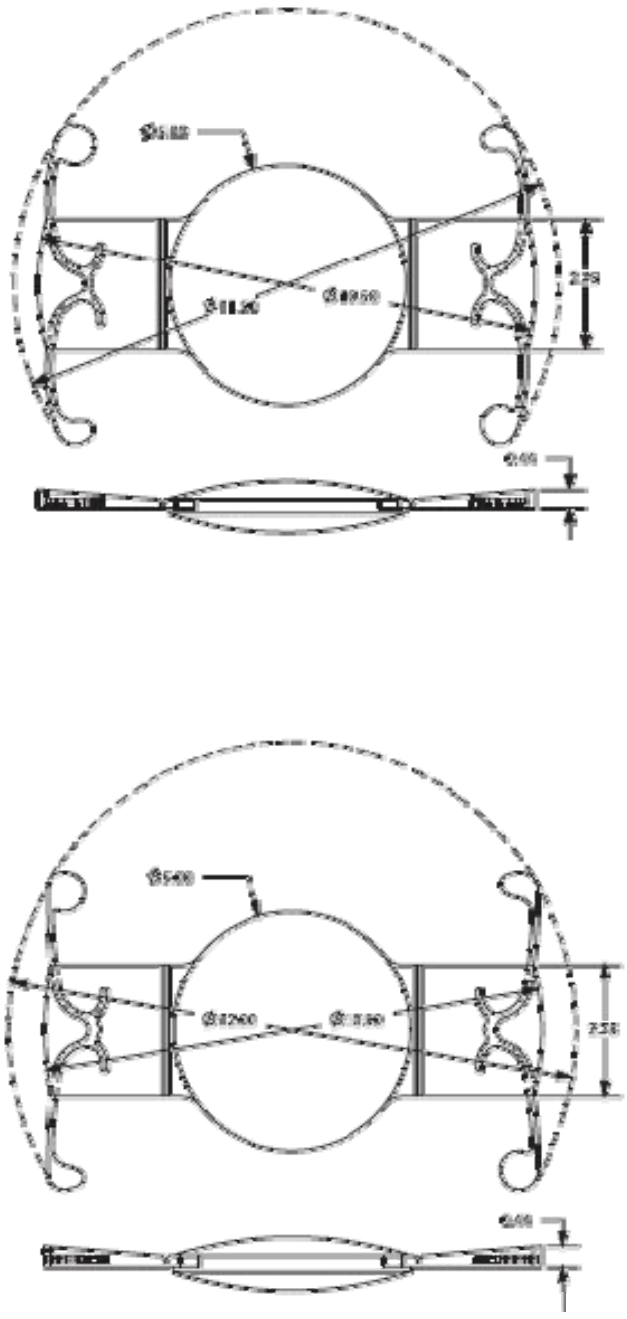

Figure 2: Absolute error in predicted postoperative keratometric axis versus preoperative corneal astigmatism